COMPARATIVE STUDY ON ESTIMATION OF ACENOCOUMAROL LEVELS IN BLOOD IN PATIENTS WITH EXTREMES OF INR VALUES AND NORMAL INR VALUES AFTER VALVE REPLACEMENT SURGERY

DISSERTATION

SUBMITTED FOR

M.D. PHARMACOLOGY

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

DEPARTMENT OF PHARMACOLOGY

PSG INSTITUTE OF MEDICAL SCIENCES & RESEARCH

PEELAMEDU, COIMBATORE- 641 004

TAMILNADU, INDIA

APRIL – 2017

PSG INSTITUTE OF MEDICAL SCIENCES & RESEARCH

COIMBATORE

CERTIFICATE

This is to certify that this dissertation entitled "**Comparative study on estimation of ACENOCOUMAROL levels in blood in patients with extremes of INR values and normal INR values after valve replacement surgery"** by Dr.D.Jeyalakshmi, is a work done by her during the period of study in the Department of Pharmacology from July 2014 to April 2017, under the guidance of Dr. S. Bhuvaneshwari M.D., Professor, Department of Pharmacology, PSG IMS&R.

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ACKNOWLEDGEMENT

I express my gratitude and sincere thanks to **Dr. S. Bhuvaneshwari M.D**, Professor, Department of Pharmacology, PSG Institute of Medical Sciences & Research, for being my guide. It was her valuable suggestions, guidance and constant encouragement in every step that has helped me to complete my research work successfully.

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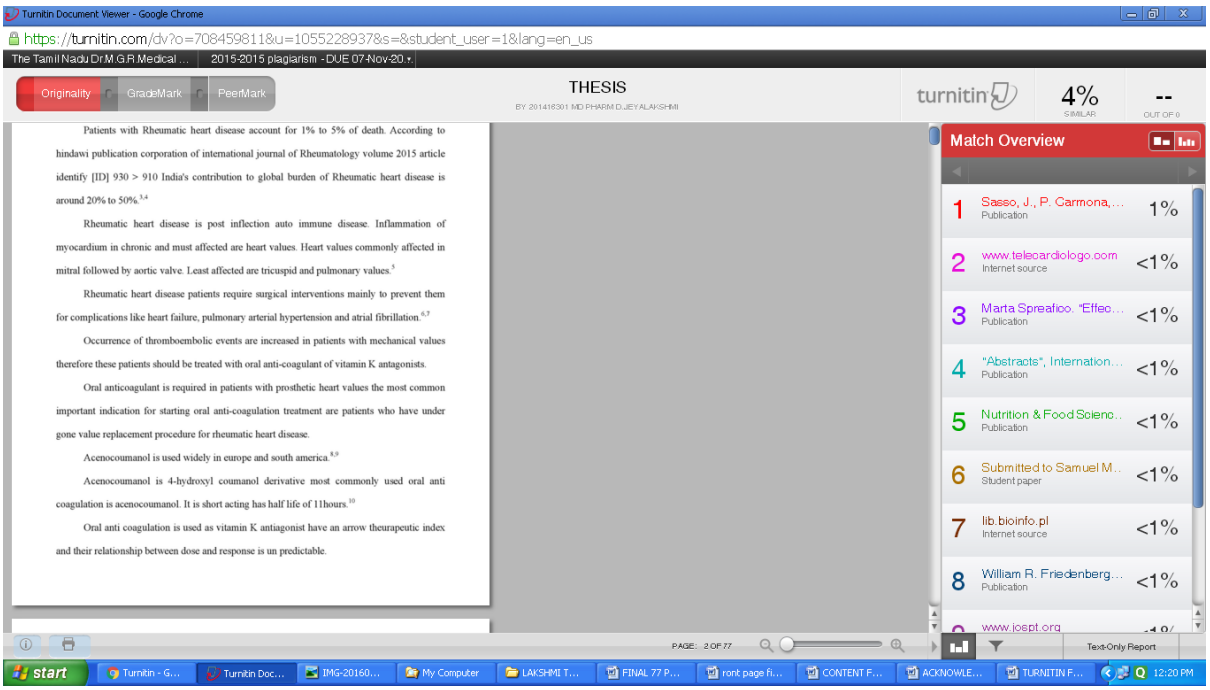
I also express my immense gratitude to the patients who consented to participate in this study.

I also thank my family members for the moral support they have rendered.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Rheumatic heart disease patients require surgical interventions mainly to prevent them for complications like heart failure, pulmonary arterial hypertension and atrial fibrillation.[6,7]
Occurrence of thromboembolic events are increased in patients with mechanical values therefore these patients should be treated with oral anti-coagulant of vitamin K antagonists.
Oral anticoagulant is required in patients with prosthetic heart values the most common important indication for starting oral anti-coagulation treatment are patients who have under gone value replacement procedure for rheumatic heart disease.
Acenocoumanol is used widely in europe and south america.[8,9]
Acenocoumanol is 4-hydroxyl coumanol derivative most commonly used oral anti coagulation is acenocoumanol. It is short acting has half life of 11hours.[10]
Oral anti coagulation is used as vitamin K antiagonist have an arrow theurapeutic index and their relationship between dose and response is un predictable.
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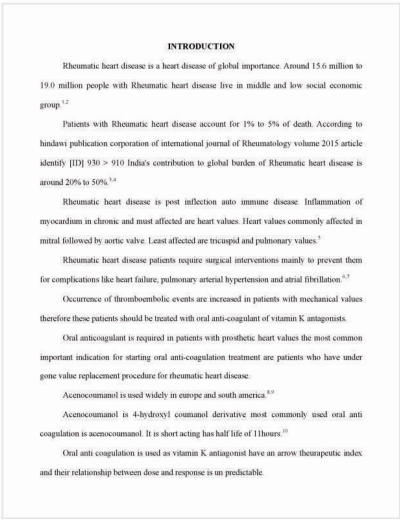

INTRODUCTION

Rheumatic heart disease is a heart disease of global importance. Around 15.6 million to 19.0 million people with Rheumatic heart disease live in middle and low social economic group.[1,2]

Patients with Rheumatic heart disease account for 1% to 5% of death. According to hindawi publication corporation of international journal of Rheumatology volume 2015 article identify [ID] 930 > 910 India's contribution to global burden of Rheumatic heart disease is around 20% to 50%.[3,4]

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PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

Recognized by The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)
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Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

To
Dr D Jeyalakshmi
Postgraduate
Department of Pharmacology
PSG IMS & R
Coimbatore

Ref: Project No. 14/406

Date: December 19, 2014

Dear Dr Jeyalakshmi,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 05.12.2014 to conduct the research study entitled "*Estimation of warfarin levels in blood in patients with extremes of INR values after valve replacement surgery*" during the IHEC meeting held on 05.12.2014.

The following documents were reviewed and approved:

1. Project submission form
2. Study protocol
3. Informed consent forms
4. Data collection tool
5. Permission letter from concerned Head of the department
6. Current CVs of Principal investigator, Co-investigators
7. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 05.12.2014 at IHEC Secretariat, PSG IMS & R between 10.00 am and 11.00 am:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Dr. P. Sathyan (Chairperson, IHEC)	DO, DNB	Clinician (Ophthalmology)	Male	No	Yes
2	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
3	Dr. S.Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
4	Dr. D. Vijaya	M Sc, Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

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Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
    a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
    b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
    c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval
    d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented
    e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented
    f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review
7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Thanking You,

Yours Sincerely,

Dr D Vijaya
Member
Institutional Human Ethics Committee

SECRETARY
PSG IMS&R
COIMBATORE-641004.
INSTITUTIONAL HUMAN ETHICS COMMITTEE

PSG Institute of Medical Sciences & Research
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January 5, 2015

To
Dr D Jeyalakshmi
Postgraduate
Department of Pharmacology
PSG IMS & R
Coimbatore

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 2nd January, 2015 in its expedited review meeting held at IHEC Secretariat, PSG IMS&R, between 10.00 am and 11.00 am, and discussed your request to change the title of your study and drug name for your study entitled:

"Estimation of warfarin levels in blood in patients with extremes of INR values after valve replacement surgery "

The following documents were received for review:

1. Your letter dated 02.01.2015
2. Protocol version 1.1
3. Informed consent forms version 1.1
4. Revised budget

After due consideration, the Committee has decided to approve the following:

1. Change of title as '*Comparative study on estimation of acenocoumarol levels in blood in patients with extremes of INR values after valve replacement surgery*'
2. Inclusion of additional arm
3. Change in drug (Acenocoumarol instead of warfarin)

The members who attended the meeting held on at which your proposal was discussed, are listed below:

Name	Qualification	Responsibility in IHEC	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
Dr P Sathyan	DO, DNB	Clinician, Chairperson	Male	No	Yes
Dr S Bhuvaneshwari	M.D	Clinical Pharmacologist Member - Secretary	Female	Yes	Yes
Dr. S.Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
Dr D Vijaya	Ph D	Member – Basic Scientist	Female	Yes	Yes

This Ethics Committee is organized and operates according to Good Clinical Practice and Schedule Y requirements.

Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable prospectively to ongoing studies approved prior to such revisions.

Kindly note this approval is subject to ratificatio in the forthcoming full board review meeting of the IHEC.

Yours truly,

Dr D Vijaya
Member
Institutional Human Ethics Committee

SECRETARY
PSG IMS&R
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INSTITUTIONAL HUMAN ETHICS COMMITTEE

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Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : ihec@psgimsr.ac.in

February 27, 2015

To
Dr D Jeyalakshmi
Postgraduate
Department of Pharmacology
PSG IMS & R
Coimbatore

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 27th February, 2015 in its expedited review meeting held at IHEC Secretariat, PSG IMS&R, between 10.00 am and 11.00 am, and discussed your request to collect blood twice for your study entitled:

"Comparative study on estimation of acenocoumarol levels in blood in patients with extremes of INR values and normal INR Values after valve replacement surgery"

The following documents were received for review:

1. Amendment reporting form dated 20.02.2015
2. Informed consent forms version 1.1
3. Medication history review form

After due consideration, the Committee has decided to approve the above amendment.

The members who attended the meeting held on at which your proposal was discussed, are listed below:

Name	Qualification	Responsibility in IHEC	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
Dr P Sathyan	DO, DNB	Clinician, Chairperson	Male	No	Yes
Dr S Bhuvaneshwari	M.D	Clinical Pharmacologist Member - Secretary	Female	Yes	Yes
Dr. S.Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
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Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Yours truly,

SECRETARY
PSG IMS&R
COIMBATORE-641004.
INSTITUTIONAL HUMAN ETHICS COMMITTEE

Dr D Vijaya
Member
Institutional Human Ethics Committee

CONTENTS

INTRODUCTION

Rheumatic heart disease is a heart disease of global importance. Around 15.6 million to 19.0 million people with Rheumatic heart disease live in middle and low social economic group.[1,2]

Patients with Rheumatic heart disease account for 1% to 5% of mortality all around the world. India's contribution to global burden of Rheumatic heart disease is around 20% to 50%.[3,4]

Rheumatic heart disease is post infection auto immune disease. Chronic Inflammation of myocardium leads to the damage of the heart valves. Mitral valve is affected most commonly followed by aortic valve. Least affected valves are tricuspid and pulmonary valves.[5]

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Occurrence of thromboembolic events are increased in patients with mechanical valves therefore these patients should be treated with oral anti-coagulant of vitamin K antagonists. Acenocoumarol is used widely in Europe and South America.[8,9] Acenocoumarol is 4-hydroxyl coumarin derivative most commonly used oral anti-coagulation is Acenocoumarol . It is short acting and has half-life of 11hours.[10]

Acenocoumarol has a narrow therapeutic index and relationship between dose and response is un-predictable. It is difficult to predict daily maintained dose of

acenocoumarol which the range from 1 mg to 56 mg. This wide variation is dose requirement is influenced by pharmacokinetic and pharamacodynamic aspects which in turn determined by genetic and environment factors.

Because of large inter individual variation and response to acenocoumarol , this demands repeated and frequent monitoring of the international normalized ratio. The international normalized ratio of the prothrombin time is the important tool which is the standard laboratory investigation used to estimate the degree of anticoagulation and to access the need for dose regulation.[11]

The major side effects of oral anticoagulation is complications due to bleeding even when INR values are within the therapeutic range.[12]A meta-analysis was done for warfarin, acenocoumarol and phenprocoumon showed that therapeutic drug monitoring of oral anticoagulants will ensures an optimal net benefit for the patients. Therapeutic drug monitoring is essential to first estimate the drug level is plasma and then according to the plasma concentration of acenocoumarol , dose can be adjusted depending on individual patients.[13]

With this background the aim of our study is to compare INR with plasma concentration of acenocoumarol taken at trough and C max levels of Acenocoumarol in blood for optimal dosage to prevent sub-therapeutic/ supra-therapeutic drug therapy leading to life-threatening complications in patients with mechanical heart valve replacement of patients

AIM

To study the association between acenocoumarol levels in blood and INR values in patients who have undergone cardiac valve replacement.

OBJECTIVE

1. To find out the trough and peak levels of acenocoumarol in blood in patients with normal INR (2.5-3.5) and patients with extremes of INR (1.5-2.5 and 3.5-4.5).
2. To find out the association between INR of three groups (low, normal and high INR) and their respective plasma concentration of acenocoumarol taken at trough and Cmax concentration.
3. To compare between trough plasma concentration of patients with low and high INR with trough concentration of patients with normal INR.
4. To compare between Cmax plasma concentration of patients with low and high INR with Cmax concentration of patients with normal INR.
5. To compare the trough plasma concentration of acenocoumarol of patients with INR 1.5-4.5 (all the three groups)
6. To compare the Cmax plasma concentration of acenocoumarol of patients with INR 1.5-4.5 (all the three groups).

REVIEW OF LITERATURE

RHEUMATIC HEART DISEASE (RHD)

RHD is one of the preventable heart disease .Rheumatic heart disease is the most common cause of mortality in patients with heart disease. RHD is rare in developed countries. In the high economic countries patients with RHD are usually migrants.[1] Social and financial alterations in developing countries have a positive outcome but major drawback is burden of disease in this area has been doubled. In these developing countries there is a good improvement in health systems. But prevalence of communicable and non – communicable disease plus tobacco addiction, diabetes, hypertension and heart disease has drastically increased.[14]RHD occurs as consequence of infection by Streptococcus pyogenes causing permanent damage to heart valves due to aberrant immune response .[15]

PREVENTION OF FIRST EPISODE STREPTOCOCCAL INFECTION

In 1995 committee was formed for preventing Rheumatic pyrexia. Group A beta streptococcus (GAS) and tonsillopharyngitis (strep throat) usually determines repeated infection of Rheumatic fever. First step in preventing Rheumatic fever is done by detection and diagnosis of Rheumatic fever as early stage. Also by initiating appropriate antibiotic cover. Proper anti-biotic cover helps in preventing secondary occurance.[16 17 18 19 & 20]

DIAGNOSIS OF STREPTOCOCCAL INFECTION

Symptoms suggestive of Group A Beta Streptococcus are rapid onset sore throat, pain during swallowing, pyrexia in high degree with headache, abdominal discomfort, also vomiting sensation and vomiting especially in children. Added symptoms are erythema in tonsillopharyngeal area, lymphadenitis in anterior cervical region, petechial in soft palate with rash as scarlatiniform. Clinical finding in children are usually not reliable and present with discharge from nose.

Only detailed history with clinical examination can guide physicians to differentiate GAS pharyngitis from pharyngitis produced by other pathogens. Throat culture or test like rapid antigen detection done by microbiological confirmation are required to conclude the diagnosis as GAS pharyngitis.

Compared to children, adults have lower incidence for GAS infections. Risk for first attack of acute rheumatic fever is low in adults when compared to children, recent suggesting are clinical symptoms can be used to confirm a case of GAS pharyngitis in adults but this criteria cannot be followed in children.[21] Irrational antibiotic treatment in adults who are not infected with streptococcal pharyngitis is not advisable.[22 ,23,24]

CULTURE FROM THROAT

Diagnosing from culture obtained throat is the traditional method used to confirm GAS pharyngitis. Good swab obtained from posterior pharynx and the tonsils in patients with GAS pharyngitis and in these patients if they did not get

appropriate antibiotic cover, their culture will be strongly positive. This positive culture will help physician to come to conclusion.

IDENTIFICATION OF ANTIGEN

For identification antigen of GAS multiple tests are available. Some tests are specific, but sensitivity of these tests were found to be minimal. In patients with sudden onset of sore throat have rapid antigen detection testing positive, confirms GAS pharyngitis which is long duration. But if rapid detection test is not positive, clinicians cannot come to conclusion if pharyngitis caused by GAS is present.[22, 25]

Detection of antigen using blood agar plates was found to be more accurate. Shortly advanced tests are identified for identification of antigen, when compared with test like rapid antigen detection.[26, 27] Clinicians are trying to find out whether blood agar or rapid antigen detection testing is more appropriate from their results and neglecting culture from throat.

TESTING ANTIBODIES FOR STREPTOCOCCAL INFECTION

Detection of antibodies for streptococcal infection were done in olden days. This test gives immune reaction which took place long time before. This method of antibody detection is deficient in diffenciating whether patient is carrier of GAS infection in pharynx or positively affected by infection. But if this antibody values are positive and elevating will help us to come to idea that individual is suffering with pyrexia of rheumatic in origin. Assays identifying antibodies like antistreptolysin O

and another antibody like antideoxyribonuclease B are routinely used. By doing this procedure clinicians can find out that whether person is a case of acute glomerulonephritis or a case rheumatic fever which is acute in origin. Antibody which is detected initially is antistreptolysin O.Antideoxyribonuclease B values are done only if first test is negative. Initial antistreptolysin O are elevated within one week after infection and reaches high value by around 3 to 6 week of infection. Both laboratory values are high even after GAS which are not complicated. Identification of both antibodies test is by assays like neutralization. But recent procedures like latex agglutination are nephelometric. Only traditional have efficient standard values than recently developed investigations.[28, 29]

Clinicians should know positive and draw backs of these lab tests which will guide them in coming to conclusion. One more investigation is slide agglutination which is used for identifying antibodies, main drawback for this is proper standardsation is not available. So this investigation is neglected now. Anti-deoxy ribonuclease B titres begin to rise 1 to 2 weeks and peak 6 to 8 weeks after the infection. Elevated titres for both tests may persist for several months after even uncomplicated GAS infections. [30, 31]

APPROPRIATE TREATMENT FOR RHEUMATIC FEVER

Efficient treatment is needed for treating rheumatic fever. Criteria to be considered while treating are symptoms and bacterial capability. Treating clinicians must have sound idea about the spectrum covered by selected drug and possible

adverse drug event that agent is capable. It is difficult to find a combination which can completely clear GAS from pharynx. But it has been proved beta lactam agents like penicillin and cephalosporins can be used for GAS infection. Usual drugs used are benzathine penicillin and penicillin V, unless patients are sensitive to these drugs. Repository penicillin which is given intramuscular, demonstrated to prevent first attack of rheumatic fever which is rapid in onset.[32, 33]

Drug with narrow spectrum, good capability and cost effective is penicillin.9 days after onset of acute illness, penicillin if started guard's against primary onset of rheumatic fever.[34]

Diagnosis done early by rapid antigen test and initiation of therapy will decrease contagious period and help person to do normal task early .If one day or 24 hours antibiotic cover is over then that patient is said be non-infectious.[35]

ROLE OF ORALPENICILLINS

Penicillin V and amoxicillin are commonly used. Trials have shown penicillin V dose used 40mg / kg, which should not be more than 750 mg in patient who weighs 27 kgs in one day is given in three doses. Dose for children is 250mg given twice a day.[36, 37] Even though patients are not symptomatic They are advised to take medications for at least 10 days.

DEVELOPMENT OF RHEUMATIC HEART DISEASE

Repeated episodes of Rheumatic fever causes the damage to the heart valves which results in Rheumatic Heart Disease. The affected valves become scarred and stretched which prevents them from moving normally, resulting in stenosis or regurgitation. Type of lesion and severity of the disease among the affected individual are determined by several factors. The key determination of disease pathogenesis in Rheumatic Heart Disease are the genetic susceptibility and environmental factors like low socioeconomic status. The effect of environmental factors on the pathogenesis of the disease varies from one population to another population. Symptoms of Rheumatic Heart Disease depends on the value affected and its severity. Symptoms due to Rheumatic Heart Disease occurs only when the valvular disease becomes severe. [38]

Patient is said to be positive for Recent GAS infection if the patient has throat culture which is positive, raised levels of anti-streptococcal anti-bodies will denote of recent scarlet infection.

Early detection and diagnosis of Rheumatic heart disease is important to prevent progression of this valvular disease of heart.[38]

RHEUMATIC HEART DISEASE AND SYMPTOMS

Patients with rheumatic heart disease frequently have symptoms like breathing difficulty, feeling tired and signs of failing heart. [38]

DIAGNOSTIC CRITERIA FOR RHEUMATIC FEVER

For the diagnosis of rheumatic heart disease according American Heart

Association modified Dr T Duckett Jones major and minor criteria are used which are given below,

Major criteria

- Carditis
- Arthritis
- Sub cutaneous nodules
- Erythema marginatum
- Chorea

Minor criteria

- Fever
- Arthralgia
- Elevated sedimentation rate
- C reactive protein
- Prolonged PR interval in electrocardiogram [39].

RHEUMATIC HEART DISEASE AND COMPLICATIONS

Repeated Rheumatic fever leads to damage valves in heart and causes Rheumatic Heart Disease. Valves become stretched and tight which resists the movement to cause regurgitation or stenosis. If the above condition missed and appropriated drug therapy neglected will cause heart failure and premature mortality. [38]

FREQUENT PROBLEMS IN RHEUMATIC HEART DISEASE

Patients with Rheumatic heart disease should be treated to prevent complications. The patients with untreated Rheumatic heart disease have the compilations like, heart failure (46.9%), pulmonary hypertension (32.7%).atrial fibrillation (13.9%). rheumatic fever causing frequent acute infection and finally inflective Endocarditis (4.5%) .

VALVES AFFECTED

The most common valves affected by rheumatic heart disease are

1, Mitral (70%)

2, Aortic valves (30%)

The frequent valve lesion are mitral regurgitation, mitral and aortic regurgitation, mitral stenosis and mixed valve disease are next common lesions [6]

RHEUMATIC HEART DISEASE AND ACENOCOUMAROL

In patients with Rheumatic Heart Disease the following are the indications for oral anticoagulant therapy:

- Rheumatic valve Disease
- Mitral valve disease
- Aortic valve disease
- Mitral stenosis
- Mitral regurgitation
- Mixed aortic and mitral valve disease.

The main indication of oral anticoagulants in Rheumatic Heart Disease is to prevent thromboembolic events which may lead to serious complications like stroke. In this therapy vitamin k antagonist (VKA) plays a major role and available. Monitoring the dose of anticoagulant was done to increase efficacy and reduce hemorrhagic complications.

Vitamin k antagonists has limitations like slow onset of action, dose requirement which is variable, polymorphism which is common influencing pharmacodynamics or protein binding pharmacokinetic of VKA, dietary vitamin k intake found different, drug drug interactions is usually multiple. Even though vitamin k antagonists had many limitations, these are drugs used for treatment of patients with valvular heart disease with artial fibrillation and cardiac valves which are mechanical.

Commonly used VKA

- Warfarin
- Phenprocoumon
- Acenocoumarol

INTERNATIONAL NORMALIZED RATIO AND RHD

Patients with valve disease have increased risk of clot formation and embolism which finally leads to stroke. For prevention of this complication anti-coagulant therapy is needed. Therapy with anti-coagulation blocks clotting and reduces occurrence of stroke. Anti-coagulation therapy dose is adjusted by estimating inter-national normalized ratio (INR).INR compares clotting times in patients who are on

anti-coagulation treatments with that of normal person's efficiency and therapeutic dose of anti-coagulation depends on linear maintains of INR [39,40,41].

MANGEMENT OF ADVANCED RHEUMATIC HEART DISEASE

Aortic and mitral valves are commonly affected by RHD. Next valve is tricuspid valve and finally pulmonary valve rarely affected .Atrial fibrillation occurs in high frequency in patients with Rheumatic heart disease which causes serious complication like emboli. Therefore patients with RHD required surgery. Mechanical valve and bio prosthetic valve are two procedures in RHD .The type of replacement surgery for a patient with Rheumatic heart disease depends on patient and health practitioner's choice, disease condition and demographic factor.[42]

ADVANTAGES OF MECHANICAL VALVE REPLACEMENT

The patients with rheumatic heart disease should be operated to prevent complications. Of the surgeries mechanical valve replacement is the surgery mostly preferred. The advantages of mechanical valve replacement are long term durability, therapeutic anti-coagulant range can be maintained and chances of later re-operation is minimum. [42]

VALVE REPLACEMENT AND ACENOCOUMAROL

Acenocoumarol and warfarin are effective in the treatment and prevention of thromboembolic disorders in the cardiac valve replaced patients. The coumarin derivative commonly used in many countries is acenocoumarol . Several factors

alters the individual response to oral anticoagulants. These includes,

THE TWO MAIN FACTORS

1) GENETIC

2) AND NON-GENETIC

THE NON-GENETIC DETERMINANTS ARE

- Age
- Gender
- Body mass index (BMI).
- Diet
- Concurrent medication
- Intake of vitamin K.
- Patients compliance [43]

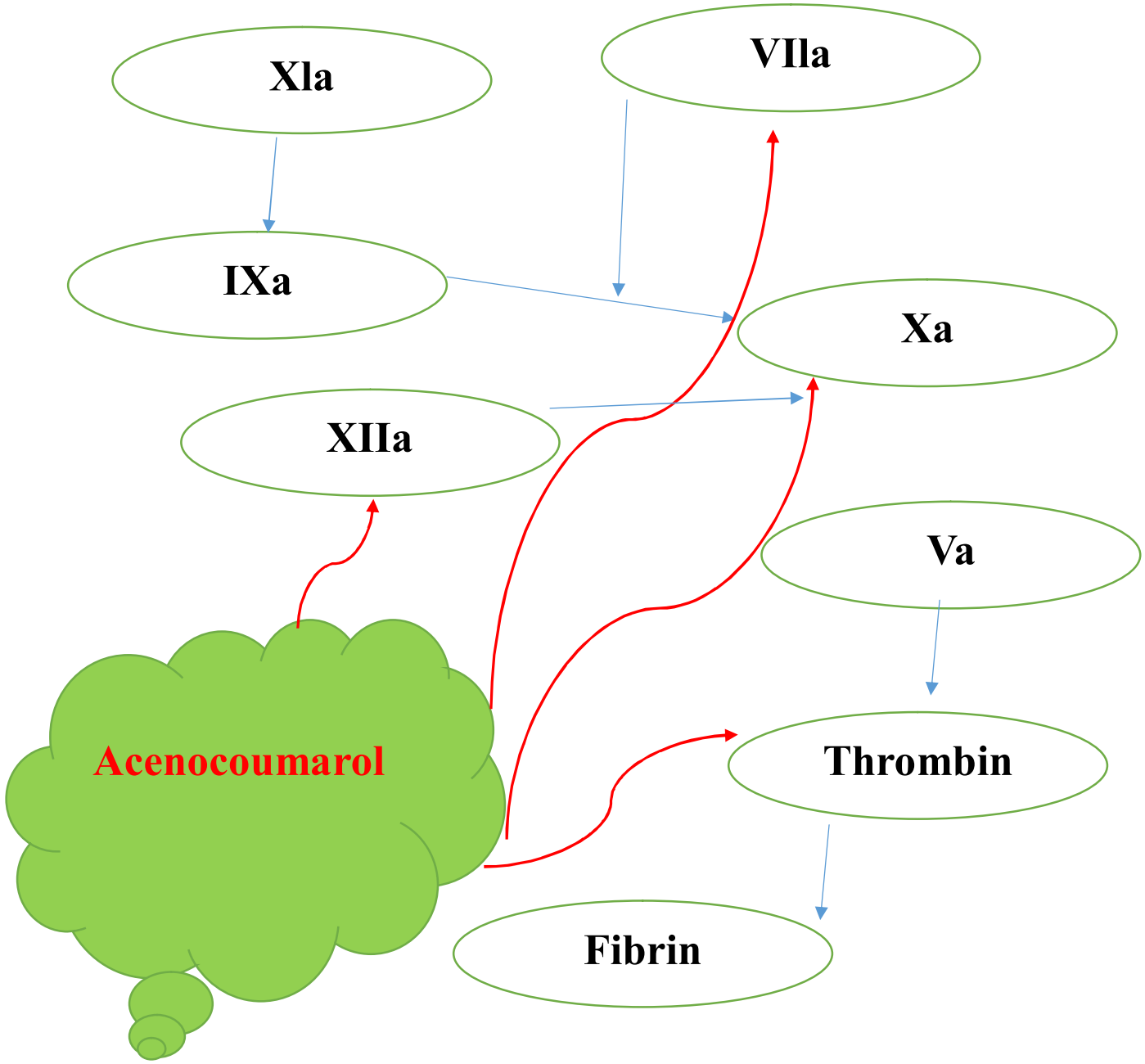
Acenocoumarol is an anti-coagulant effective in treating and preventing thromboembolic events in the cardiac valve replaced patients.[44]

ACENOCOUMAROL

The oral anticoagulant used worldwide are vitamin K antagonists. Vitamin K antagonists act by inhibition of vitamin k epoxide.[44]

Acenocoumarol is the commonly used vitamin K antagonists.[8,9] Anti-coagulant Acenocoumarol inhibits action of vitamin K on gamma acid-carboxylation of certain glutamic acid molecules, located in the coagulation factor II (Pro-Thrombin) , VII , IX , X and protein C and S in the liver. Because of this inhibition no blood clotting can be initiated.

TARGET SITES OF ACENOCUOMAROL



KEY

CLOTTING CASCADE

ACENOCOUMAROL

Acenocoumarol rapidly absorbed from the gastro- intestinal tract, peak concentration (Cmax) of 0.3 mcg/ml in 2-3 hours. Acenocoumarol is highly bound to serum proteins and only 1.52% of the drug is free. [44]

Bioavailability – 96%

Protein binding – 98%

Metabolism – hepatic (mainly through CYP2C9)

Terminal elimination half-life – 8- 11(shortest)

Excretion- mostly renal.

Patients with polymorphism in CYP2C9 and VKORC1 had increased incidents of over anticoagulation (almost up to 74%) and decreased risk for mild anticoagulation (up to 45%). Diet containing vitamin K in form of Vitamin K_1 or phylloquinone in leafy vegetables was variable between patients and Vitamin K in form of menquinone or K_2 was produced in the colon by bacteria was also variable in patients, these varied dietary intake of vitamin K alters international normalized ratio which is the usual laboratory investigation used for evaluating the dose of vitamin K antagonists (VKA). Therefore recommendations about diet was given to patients who were on VKA.[44]

DIFFERENCE BETWEEN ACENOCOUMAROL AND WARFARIN

Acenocoumarol is completely and rapidly absorbed from stomach. Acenocoumarol and warfarin are structurally different. Nitro group in para position in phenyl ring is the difference. It was proved that acenocoumarol has good

performance rate in maintaining International Normalized Rate within therapeutic range when compared with warfarin. [44].

ONSET OF ACTION OF ACENOCOUMAROL

Acenocoumarol has rapid onset of action, with 15-20 hours of duration of action. Hypoprothrombinemia caused in most of patients is almost after 36 hours after the first dose of acenocoumarol . Even though half-life of acenocoumarol is short, after attaining steady state pharmacodynamics feature is found to be stable. Around 1.52 % of drug is only free in plasma .Remaining is highly bound to serum proteins. After drug is given orally maximum raise in prothrombin time is seen 24 – 30 hrs.[44]

SAFETY AND EFFICACY OF ACENOCOUMAROL

Safety and efficacy of acenocoumarol has been studied in varied conditions requiring treatment and prophylactic treatment of thromboembolism like

1. Atrial fibrillation
2. Cardiac valve replacement [38]

Thromboplastin time test is prolonged from 36 to about 72 hrs depending on the therapeutic dosage given to that individual. When drug is withdrawn thromboplastic-time returns to normal. The dose of Acenocoumarol ranges from 1 to 8 milligrams. Usual starting dose of Acenocoumarol is 2mg for person within normal weight range [45].Acenocoumarol is rapidly absorbed after ingestion with 60% minimum as systemic bioavailability. Cmax is

reached within 1-3 hrs.' after the dose. AUC valves of plasma-concentration versus time in proportional to dose given. Most of drug remain bound to plasma protein (98.7) that is albumin. Acenocoumarol is primarily metabolized by CYP2 C9 enzyme. Secondly by CYP1 A2 and CYP2 C19 Plasma half-life is 6.26 to 14.22. Anti-coagulant activity of R (+) enantiomer. Dose excreted in urine is about 0.12 - 0.18% which is unchanged in urine. Excretion of cumulative metabolites of unchanged active substance takes approximate period of 8 days. Of which is 60% dose in urine and 29% of dose in faeces [46].

ACENOCOUMAROL DOSE

To maintain Acenocoumarol dose with in therapeutic range the following were considered,

- Demographic Data.
- Indication of Anticoagulation therapy.
- Concurrent Medication.
- Diet (Vegetarian or Non-Vegetarian).
- Any episodes of bleeding.
- Most important INR target range.

Acenocoumarol is one of life saving drug. But therapeutic index in narrow. Major adverse effect is increased risk for profuse bleeding. To prevent this serious side effect regular and repeated measurement of International normalized ratio (INR)

of prothrombin time is a must during treatment with Acenocoumarol . Commercially available Acenocoumarol is racemic mixture of roughly equal amount of (R) and (S) Enantiomers. S acenocoumarol is more patient enantiomer. It almost tenfold higher when compared to R-acenocoumarol . Elimination half-life of S-acenocoumarol in substantially shortened (1.8h) while R-enantiomer (6.6h) reaches much higher concentration in plasma when compared with later .Because of the above reason anti-coagulation effort is mostly due to R-acenocoumarol , even though S-acenocoumarol has better intrinsic anti-coagulant activity [47,48].

Enantiomers of Acenocoumarol differ in pharmacodynamics and pharmacokinetics features but Racemic Mixtures contain equal parts of R (+) and S (+) enantiomers. Measurement of Acenocoumarol in plasma can be done by using non-enantiomers assay [46].

FACTORS INFLUENCING EFFECTS OF ACENOCOUMAROL IN A PATIENTS

There are varied factors affecting the effect of acenocoumarol drug in patients. These are the following important factors.

- Polymorphism [Genetic]
- Non-Genetic
- Ethnic
- Still unknown reasons

GENETIC INFLUENCES

Well known genetic factor contributing to variation of Acenocoumarol therapeutic dosing CYP4F2 genes. Gene polymorphism plays an important role in dose requirements of Acenocoumarol .The contribution of gene polymorphism is influencing dose of Acenocoumarol within therapeutic range was also evaluated in North Indian valve replaced patients.

NON-GENETIC FEATURES

Age, gender, BMI (Basal Metabolic Index), intake of vitamin K, concurrent medications and compliance of patient are the non-genetic factors which alters the acenocoumarol dose in the paients.[49]Influence of age on dosing of Acenocoumarol is varied. Activity of cytochrome (P450) enzyme in body reduces with advancement of age which resulted decrease in Acenocoumarol dose is elder patients. Decreases in 0.5 to 0.7 mg per 10 yrs. which independent of genetic polymorphism and height of patient, while an opposite trend was elicited in other group of patients [50]

In a study done in North part India it was proved that dose is decreasing with increase in age. But this finding was not significant statistically. (P=0.47). Another finding in this study was sex of patient did not significantly after dose requirements of Acenocoumarol . But there are studies to prove that female patients required quite large dose of daily maintenance dose of Acenocoumarol . But these are studies which showed Acenocoumarol dose did not vary according to gender [51].

Acenocoumarol dose was influenced by drug drug interactions. To obtain stable constant anti-coagulation above factor should also be considered [49].Co-administered medications which plays important part in medication for patients was also evaluated, it was found that patients on Amiodarone as concurrent medication did not show significant variation in Acenocoumarol dose (P=0.12) .Patient on atorvastatin also showed the similar finding (P=0.5) But physician must be cautious in interpreting above result because patients on Amiodarone and Atorvastatin group was minimum. But these studies which proved using statin with Acenocoumarol caused slight reduction in dose in daily routine dose of later [50].

There are also studies showing co-administered drugs did not cause significant changes in Acenocoumarol maintains dose. No difference was seen in Acenocoumarol therapeutic dose in patients with concurrent medication and those without any added drugs [52]. Consumption of diet rich in vitamin K (e.g.: Green Vegetables) will cause reduction in anti-coagulant efficacy [53].

Flora of gut is altered by initiation of some antibiotics which will result in exaggeration of anti-coagulant repose to coumarins [54].One of parameter included in prediction of dose of Acenocoumarol is BMI. But study done in Northern part of India which grouped patients into two groups according to BMI elicited that no significant correlation was found with BMI and dosing of Acenocoumarol [55].

Yet another factor determining requirements of Acenocoumarol is compliance. In a non-compliant patient dose of Acenocoumarol need to get a therapeutic repose in varying which caused longer time to reach stable INR. When

compared to patients with normal compliance [56].

INTERNATIONAL NORMALIZED RATIO (INR)

Oral anti-coagulant treatment is normally monitored by international rationalized ratio (INR). Which is followed worldwide.

Oral anti-coagulation is an important drug in patients

- After heart valve replacement.
- With Rheumatic Heart Disease.
- With Atrial Fibrillation.
- With Deep Vein Thrombosis.

Most common adverse effort in these patient on oral anti-coagulation therapy is massive hemorrhage or thromboembolism which develops when the anti-coagulant drug is not in therapeutic range. Anti-coagulation response individuals varies which makes a regular monitoring is compulsory to prevent complications. These are huge variety of parameters related to coagulation. But the parameter which directly shows rate of thrombin generation is Prothrombin Time (PT) [57].

Number of studies have shown that concentration of factor 11 (F11) is linearly related to rate of thrombin production. Prothrombin time is commonly expressed as International normalized Ratio just to avoid bias form variations among coagulation analyzers (System Derived) and source of reagent (Different batches of thromboplastic)[57] Link between INR values and various factors of coagulation is still inconsistent assaying clotting factors FII , FVI and FX frequently affects

prothrombin time (INR) protein C and Prothrombin fragments F1 + 2 had no prominent impact on variation of INR which was proved by RS Ratio of Activated Partial Thromboplastic Time (APTT) or fibrinogen [58].

Despite careful and well-organized care and frequent laboratory control, the INR of patients are not within the therapeutic range due to several interfering factors such as co-medication changes, interfering diseases and changes in diets. INR outside the therapeutic ranges are associated with an increased risk of bleeding complications or thrombotic episodes[59]

COMPLICATIONS DUE TO INAPPROPRIATE DOSE OF ACENOCOUMAROL

Most common adverse effort of anti-coagulation with oral coumanin derivatives in bleeding complication. In these patients therapeutic failures is also common. Around 2 - 5% of patients on oral anti-coagulant treatment experience serious bleeding every year. While 0.5 - 1% of patients have eposide of fatal bleed. Only because of narrow therapeutic range of INR and dose which has high variability to attain anti-coagulation is the main reasons for complications. To reach the target INR repeated INR checks are needed. Depending on INR doses are changed.

According to Gadisseur et al. patients on acenocoumarol treatment during initial first 6weeks of anti-coagulation are maintained in therapeutic range for 30% .Because of this long term to acheive stable and effective INR, adverse effects like bleeding are more common during first month of anti-coagulation initiation. Above

finding was described by landefeld et al. Episode of Bleeding and rates of thromboembolism directly correlates with time within therapeutic range.[45]

Study was conducted to confirm initial doses 2-6 mg Acenocoumarol given to patients would predict maintenance dose of oral anticoagulant therapy in terms of normal range of INR. Above study proved only around 76% of patients had INR were within adequate range. While approximately 13% of Patients had range higher than therapeutic range. 7% of patients had INR below range, all these findings were dose independent. This study proved that INR value and required dose of acenocoumarol had inverse relationship. Another additional findings in this study was anticoagulation dose for elder patients must be less when compared with youngers.[59]

The maintenance dose of acenocoumarol varies in individual patients which is determined by multiple factors as discussed above. Therefore estimation of acenocoumarol in plasma of patients will be more accurate and precise for the dose adjustment of acenocoumarol .[13]

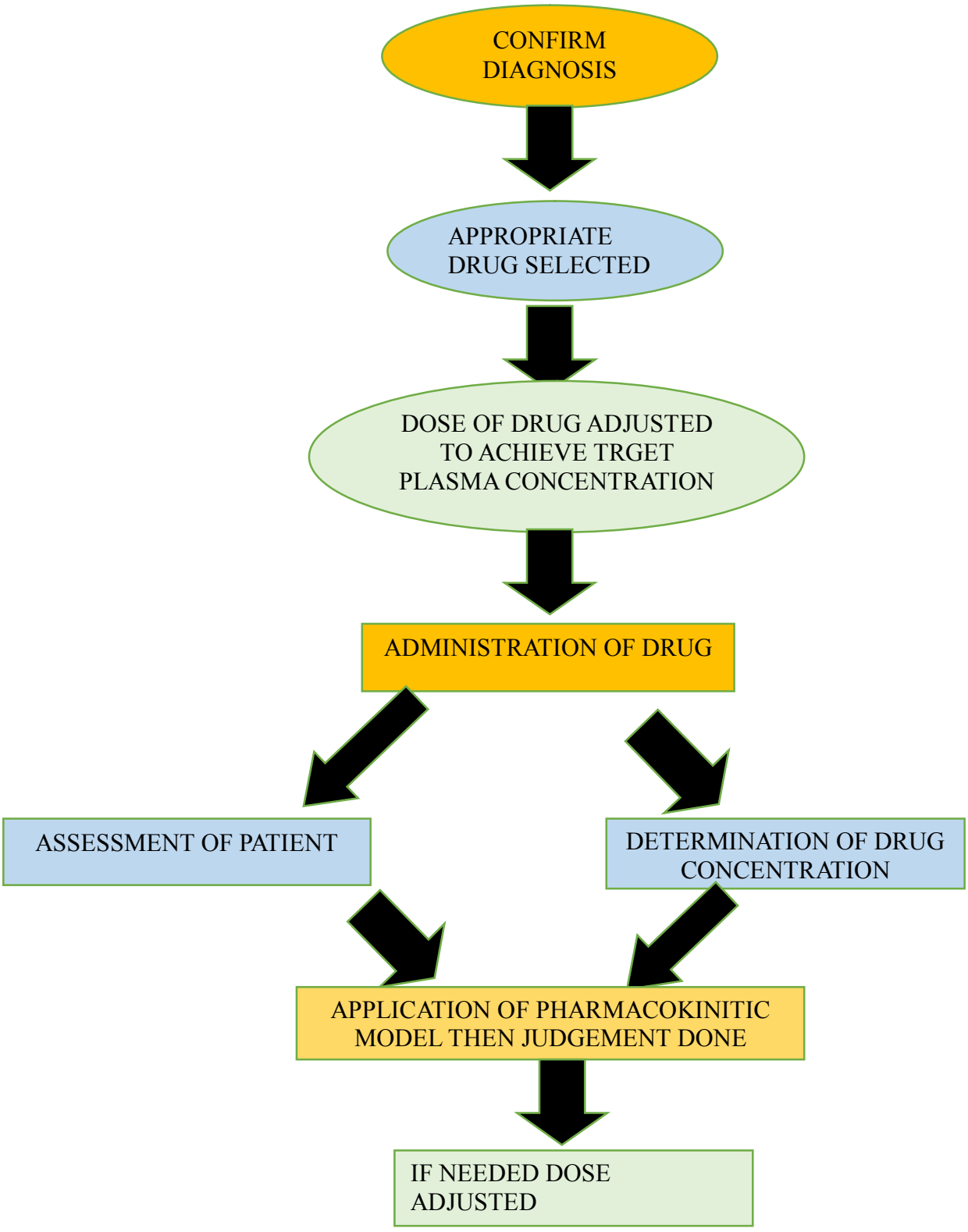
THERAPEUTIC DRUG MONITORING [TDM]

Monitoring of plasma concentration of drug for adjusting dose is called TDM.TDM helps in maintaining drug doses according to individuals by keeping plasma drug concentration in blood within therapeutic window or range.TDM helps in finding out efficacy and safety of a medication in varied number of clinical settings. This is done by combining knowledge of pharmaceutics, pharmacokinetics and pharmacodynamics. Main goal of TDM process is to formulate doses according

to individuals to get optional benefit for patient. To analyse TDM pharmacokinetic principles are used by pharmacologists and clinical pharmacists.

Clinical pharmacokinetic monitoring was supported by drug concentration – response relationship, pharmacokinetic properties were mapped, invention of computerization which was high throughout had more positive growth in analytical technology.

STEPS IN ACHIEVING DECISIONS IN DOSE WITH THERAPEUTIC DRUG MONITORING



Plasma concentration measurement will be useful, that is patients with low level shows compliance which is poor or patient is under treated. If previous estimation of plasma concentration revealed to be high or drug which is prescribed usually does not cause low concentration, then poor compliance is implicated. Measuring drug levels in blood will make physician work little easy to start drug therapy and later tailor dose according to individual.

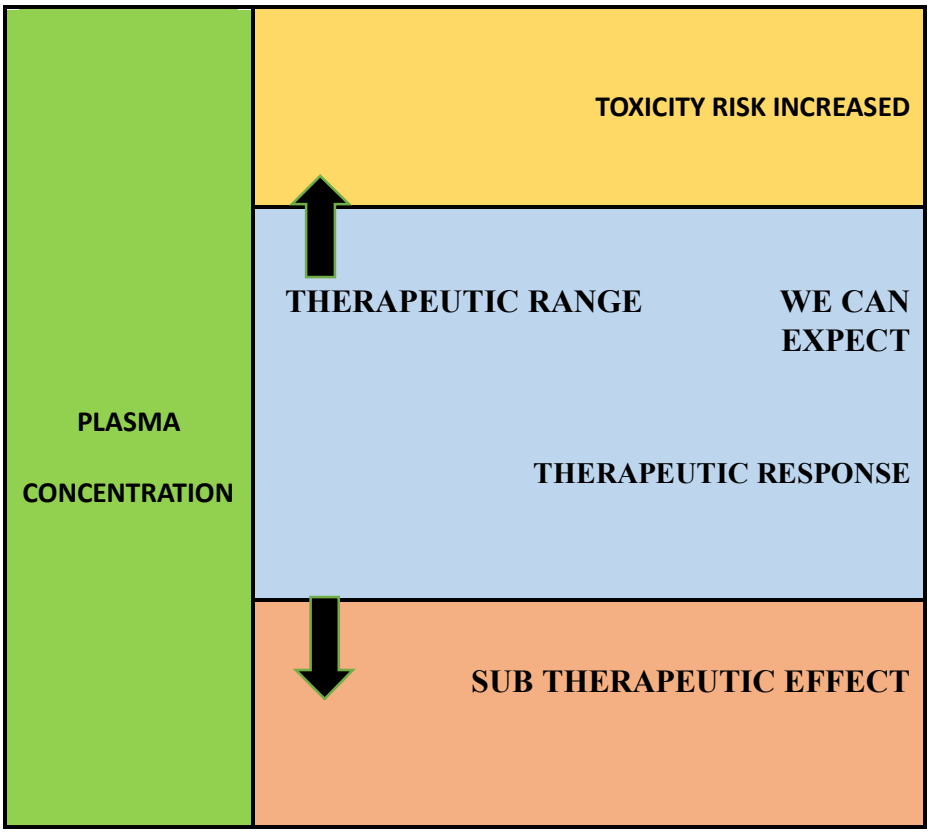
This method is important for drug with narrow therapeutic range like

- Digoxin
- Phenytoin
- Lithium
- Theophylline
- Anticoagulants
- Cyclosporine
- Aminoglycoside antibiotics.

If a need for adjusting dosage during course of treatment in patients with kidney disease, estimating blood levels will be useful. If there is a poor clinical response for a well-established disease then under treatment is considered. It will be difficult to monitor an effect when a drug is used for prophylaxis. In this stage, treating physician can choose a dose that is capable of producing target plasma concentration. This is common with preventing manic depressive attacks with lithium, to prevent

epilepsy after trauma or neurosurgery with use of phenytoin and cyclosporine which is used after transplant, to avoid rejection of transplant. In all these conditions concentration of drug in plasma is done in early stages of treatment to protect patients from toxic plasma concentration. Therefore in this case confirmation can be done by TDM.

THERAPEUTIC RANGE CONCEPT [63]



THERAPEUTIC DRUG MONITORING AND MEASURING DRUG CONCENTRATION IN PLASMA

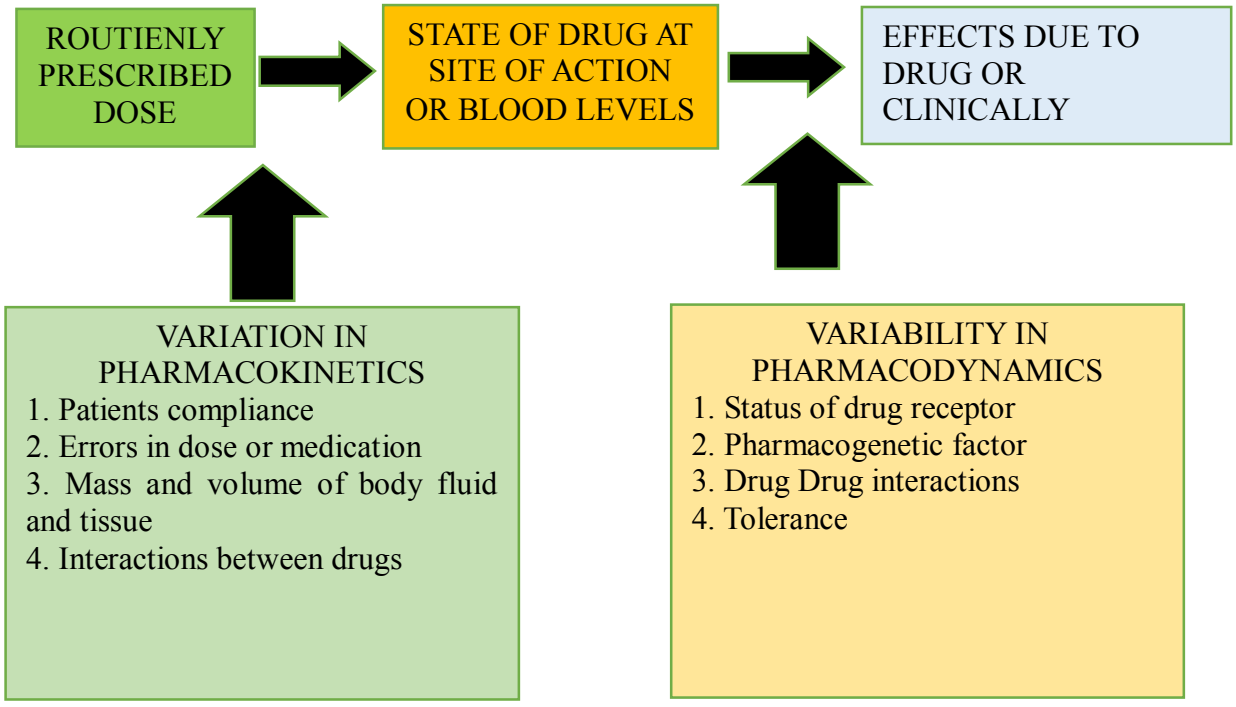
Because of the variability of pharmacokinetic differences estimating steady state drug concentration and modification of dose to reach needed concentration is effective .There are limited number of drug formulation, which has good relation

between blood levels and dose response curve. In this case measuring blood concentration will be an important surrogate index. Therapeutic drug measuring is only portion of TDM that gives perfect clinical interpretation of drug levels and this is done on pharmacokinetics base principles. To ensure full benefits in clinical cases, correct interpretation of plasma concentration is main tool.

Physicians evaluate pharmacodynamics of drug by therapeutic changes such as lipid profile blood sugar ,blood pressure and then by blood coagulation and clotting.

Main drawback is there are many drugs which does not have readily available measures or procedure. Thus stages of TDM is predicted on basis that there is strong relation between drug formulation and concentration of drug in blood. Another existing relationship is between concentration of drug in plasma and its pharmacodynamics effect.

PHARMACOKINETICS AND PHARMACODYNAMICS RELATIONS AND CONDITIONS THAT INFLUENCE THEM



THE CRITERIA A DRUG SHOULD FULLFILL FOR CONCENTRATION MEASUREMENTS IN PLASMA TO BE EFFECTIVE

- Clinical evidence that show therapeutic or toxic side effects.
- Concentration in blood level and desired or adverse effect which is toxic or both have effect relationship.
- Therapeutic range being low.
- Important active metabolites are not metabolized.

REQUIREMENTS OF THERAPEUTIC DRUGS MONITORING

Requirements of therapeutic drugs monitoring are Pharmacokinetics, Pharmacodynamics and Laboratory Analysis.

TO ATTAIN GOAL IN THERAPEUTIC DRUG MONITORING

- Identifying nature of problem to be solved.
- Appropriate matrix selected.
- Select methodology to solve the conditions.
- Valid analytical schemes developed which are performed accurately with quality which in good and interpretation within the framework of clinical problem.

STEPS TO BE FOLLOWED TO GET DEFINITIVE PLASMA CONCENTRATIONS

Care and attention must be given for timing of blood sample.

- Type of blood sample used for analysis.
- Technique used for measurement.
- Interpretation and analysis of results.

Laboratories which do drug testing routinely have developed assay procedures for high performance liquid chromatography (HPLC).

Treating clinicians should consider not only blood plasma concentration but also features which are seen clinically. Doctors must be familiar with the analysis plasma concentration of patient. Critical importance should be given to demographic characters of patient like patient's age, disease condition, ethnicity and variation in pharmacokinetics and pharmacodynamics between individuals.

PLASMA SAMPLE AND TDM

To estimate concentration in plasma accurately, team of TDM must be informed in relation to last dose given when sample was collected and when drug regimen was initiated. Life threatening complications can be solved and treated by estimating peak plasma concentrations within 1 to 2 hours after a oral dose serum concentrations of almost all drugs peaks. Conditions which cause slow or delayed absorption can significantly slow time at which serum peak concentrations are reached.

Trough blood levels are least affected by absorption and problems of distribution.

If a patient is on a drug for a long period, there is chance of drugs and metabolites to accumulate in body. It is said “steady state “is achieved when amount of drugs administered in equivalent to quality of drug eliminated. The requirement to attain this steady state depends directly on half-life of drugs. About 95% of drugs accumulates after 5 half-lives are completed, which shows steady state is reached.

If a loading dose is given blood levels which are equivalent to steady state in reached. Plasma concentrations should be monitored as often as possible when toxicity is suspected. Similarly quick and immediate assays are appropriate when of therapeutic control is poor, as in a clinical condition like atrial fibrillation, where loading dose is helpful.

Details of dose and duration of treatment are important to analyze results. For a good interpretation of blood levels which change often, the dose and time of drug taken and sample withdrawn time should be known. Since absorption varies after oral dose, blood sample must be collected in elimination phase, not in absorption or distribution phase.

These is considerable variation in people in towards.

- Absorption.
- Distribution and
- Elimination of Drugs

Drugs like

- Oral Anti-coagulant.
- Phenytoin.
- Digoxin.

Vary ten times or greater in steady plasma concentration in patients who are treated with same dose. These differences are

- Maximum due to formulation of drugs.
- Genetic variation of patients.
- Disease condition.
- Effects due to environment
- Drug interactions.

Advantages of measuring blood plasma levels

- Helps clinicians to find correct dose for that individual patients.
- To gain best therapeutic effect with reduced risk of toxicity.
- Easy to measure toxic or therapeutic effect of drugs.
- Added information about drug action can be obtained.
- This helps to tailor dosage within correct therapeutic range.

Factors which alter the efficacy of parent drug for a known blood concentration in total blood are drug interactions, electrolyte imbalance, acid base balance patients age, bacterial resistance and capacity of protein binding. For a safe and effective therapeutic medication and adjusting individual dose TDM plays a vital role.[60]

ACENOCOUMAROL AND HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

Acenocoumarol is usually monitored by prothrombin time. We have already discussed that there is no relation between INR and dose of acenocoumarol and estimation of acenocoumarol levels in plasma will be the appropriate method to monitor dose of drugs, Because INR can be raised even when there is no significant cause or disease condition. Acenocoumarol therapeutic concentration in 32 – 39 µg/l [64]. This drug stimulates unwanted adverse efforts like bleeding if this therapeutic window in exceeded.

ADVANTAGE OF ESTIMATING ACENOCOUMAROL IN PLASMA

- Helps in diagnosis.
- Appropriate and effective treatment can be given for patient.
- We can distinguish between compliant and non-compliant patient.
- Patients with resistance to anti-coagulation treatments[61]
- To find out any pharmacokinetic interactions on acenocoumarol metabolism and / or its plasma protein binding capacity. To find out answers for these questions, correct and most sensitive analytical method is required to analysis acenocoumarol ’s stereo isomers.

HPLC methods has two stereo specific analysis methods for estimation of acenocoumarol . Using whelk-chiral stationary phase HPLC analytical method is useful in estimation of enantiomers of acenocoumarol . This study proved that HPLC

is most sensitive analytic method for determination of acenocoumarol in plasma. Performing characters of assay is most accurate and can be easily repeated. Results demonstrated by this method was found to be reliable and a procedure which is convenient for estimating plasma concentration of acenocoumarol [62, 63, 64]

Therefore we can justify our study saying that after heart valve replacement patients need chronic administration of acenocoumarol . Since acenocoumarol has a narrow therapeutic index and dose varies according to individual which depends on various factors. This leads to frequent and repeated monitoring of INR, to prevent serious adverse effects .There are studies which proves INR is not reliable. Therefore estimating plasma concentration of acenocoumarol will be more precise, accurate and reliable for dose adjustments of acenocoumarol in order to prevent complications due to oral anticoagulation.

METHODOLOGY

ETHICAL APPROVAL

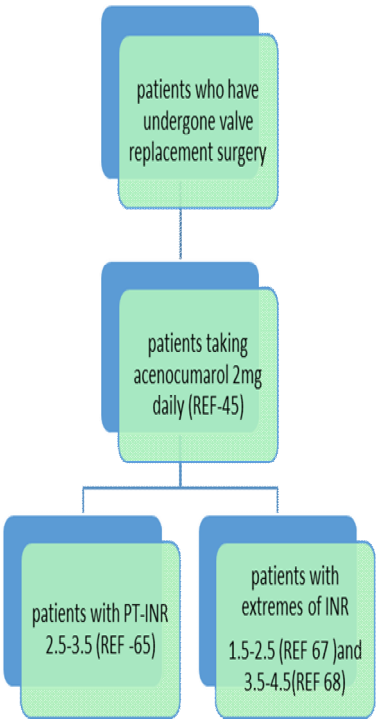
Study protocol and the written informed consent form was approved by Institution Human Ethics committee [IHEC] before starting of the study.

STUDY CENTRE

This study was done in the department of Pharmacology and the department of Cardiothoracic and Vascular surgery PSG Institute of Medical Sciences and Research in collaboration with the Pharmaceutical analysis department at PSG College of Pharmacy.

STUDY POPULATION

Outpatient from department of Cardiothoracic and Vascular surgery from 2015 February to June 2016.



INCLUSION CRITERIA

- Patients who underwent mechanical heart value replacement.
- Taking Acenocoumarol 2mg.[45]
- Once daily dose.
- INR of 1.5 – 4.5.[65]
- Patient's with normal liver function.
- Vitamin-K restricted diet.
- Patients who have completed 3 Months of post operation convalescent period.

EXCLUSION CRITERIA

- Patients who have not completed 3 Months of convalescent period after surgery.
- Patients with abnormal liver function.
- Unrestricted vitamin-K diet.
- Other major illness which lead to coagulation disturbance. [Annexure-l].
- Patients on specified drugs which are known to produce inter action with acenocoumarol . [Annexure-2]

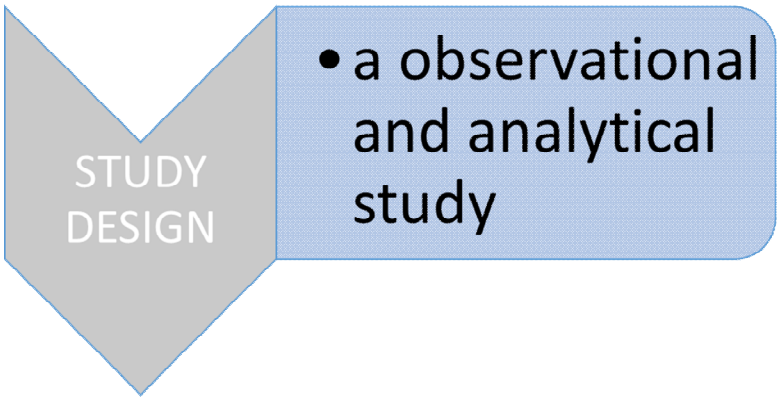
Recruitment of Participants

The details and purpose of the study protocol were explained to each participant individually and their doubts were clarified before obtaining informed consent.

The informed consents forms provided to the participants were either in English or in Tamil.

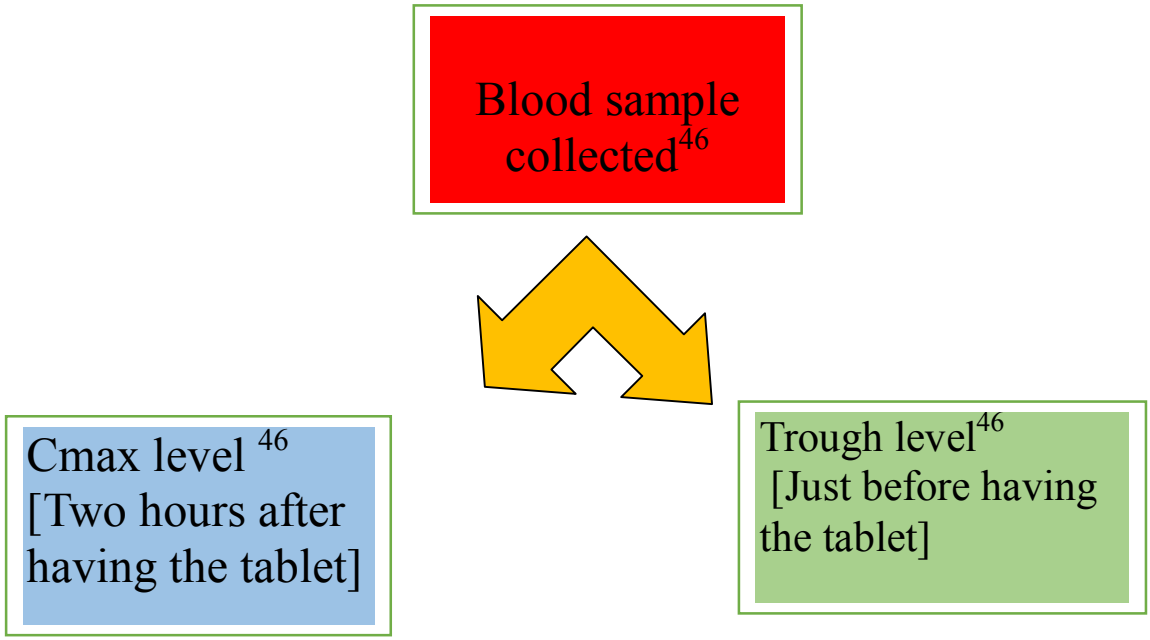
The participants who gave written informed consent and came under inclusion criteria were enrolled for the study. A copy of the consent form in attached in the annexure.

STUDY DESIGN

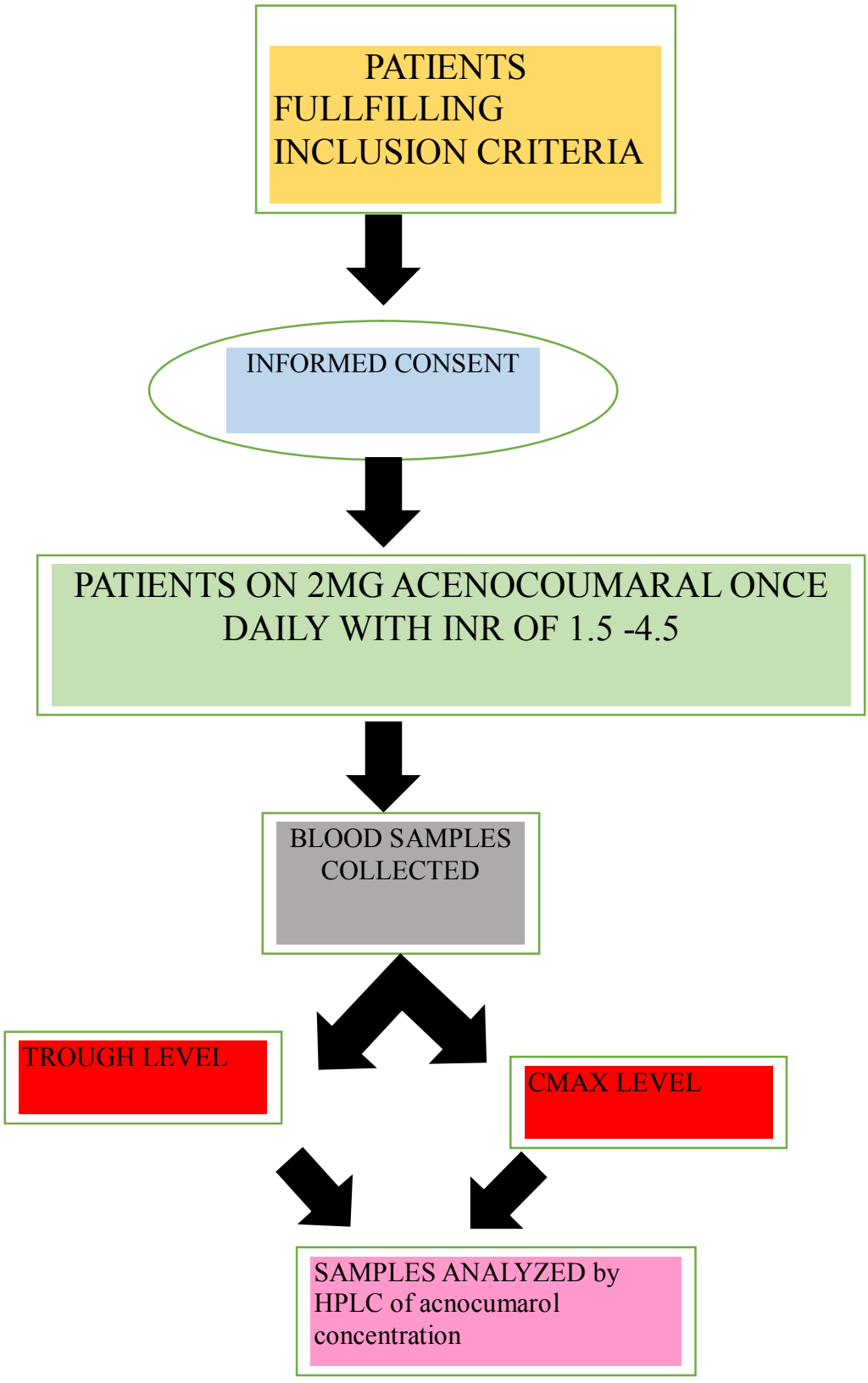


TIMING OF THE BLOOD SAMPLE

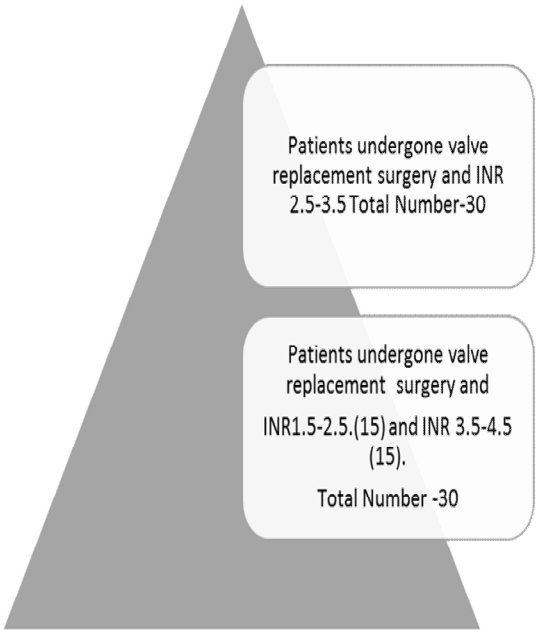
Around 2ml of blood was collected from the patients at the trough and Cmax levels.



FLOWCHART OF METHODLOGY



SAMPLE SIZE: 60 Patients. This study is a pilot study.



DEVELOPMENT OF UPLC METHOD OF HPLC FOR STANDARDISING ACENOCOUMAROL AND LATER ESTIMATION OF ACENOCOUMAROL IN THE PLASMA OF PATIENTS

Instrumentation and Chromatography conditions

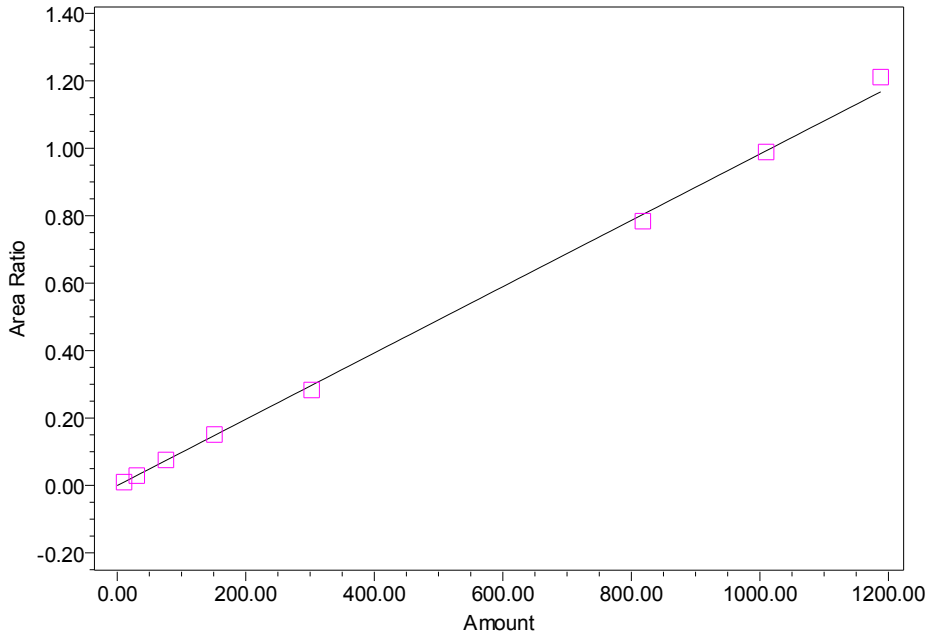
The UPLC instrument consisted of a Waters Acquity H class UPLC system equipped with a quaternary pump and 96-vial autosampler coupled with a diode array UV detector (Waters, Milford, MA, USA). The chromatographic separation was performed on an Acquity UPLC BEH C18 column from Waters (2.1 mm × 100mm; 1.7µm). The column temperature was set at 35ºC and the autosampler was kept at 10ºC. The mobile phase composed of a mixture of 25mM ammonium acetate buffer

pH 3.5 adjusted with acetic acid (70%, v/v) and acetonitrile (30%, v/v) at a flow rate of 0.3ml/min. Before analysis the mobile phase was filtered through a 0.22µm membrane filter and degassed by ultra-sonificition. A 5µl injection of each sample was loaded on to the system and total analysis time was 8 min. DAD was set at 282 nm. Data acquisition was done using Empower 3 software version 1.0 (Waters). [62 63 64]

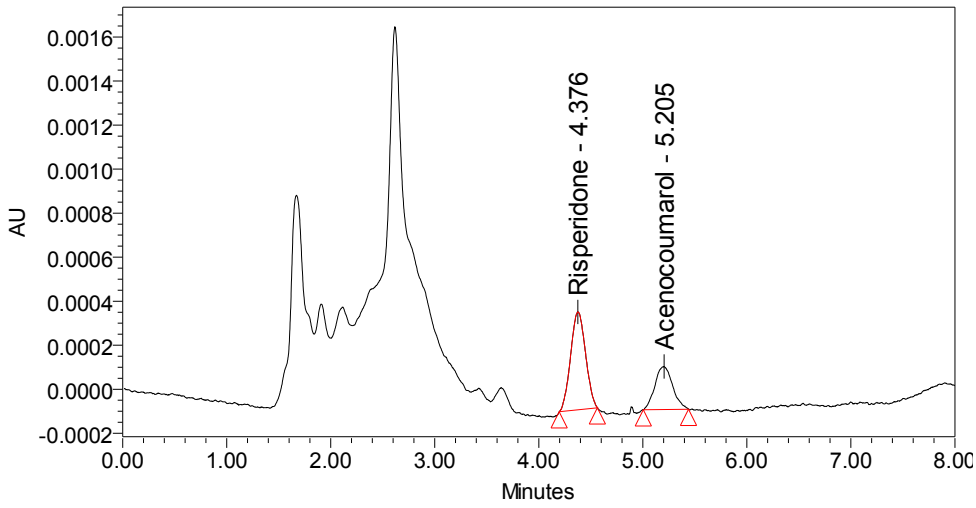
SAMPLE PREPARATION AND ESTIMATION OF ACENOCOUMAROL CONCENTRATION IN PLASMA USING UPLC METHOD OF HPLC

Sample preparation was carried out by the liquid-liquid extraction procedure and tetra -butylmethylether used as extraction solvent. Linearity was evaluated by linear regression analysis with different concentrations within the range 10 to 1200 ng/mL. The calibration curves exhibited excellent linearity with regression correlation coefficient (r^2 > 0.998) over the concentration range of 10 to 1200ng/mL. The percentage accuracy observed for the mean of back-calculated concentration for four calibration curves for the entire drug were within 95.28-103.71.

Representative Calibration Curve Plot for Acenocoumarol



Representative Chromatogram of Standard in Plasma



STATISTICAL ANALYSIS

The collected data were entered into SPSS version 19 for statistical analysis.

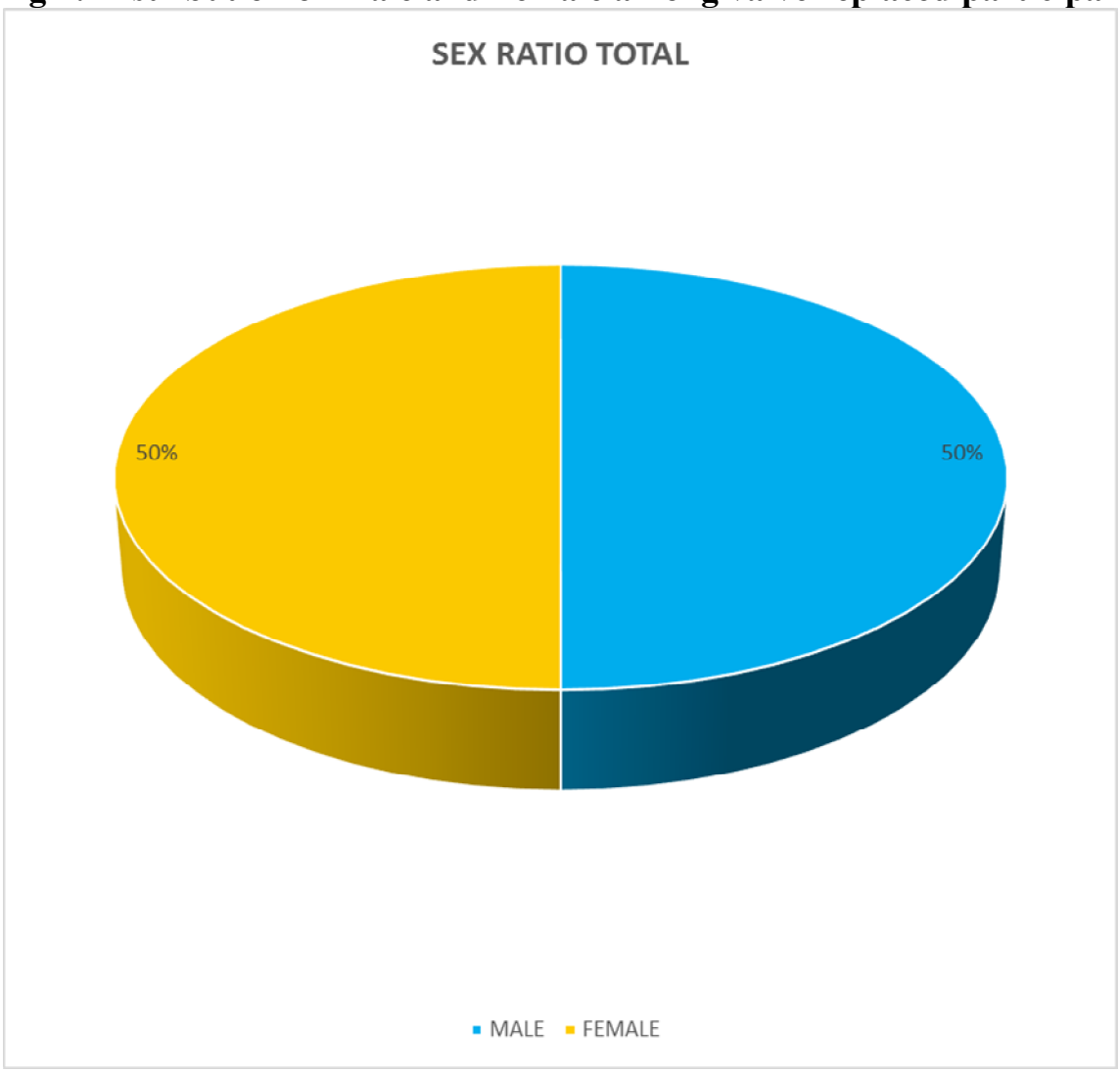
- Pearson correlation was done to see the association between INR of three groups (low, normal and high INR) and their respective plasma concentration of acenocoumarol taken at trough and Cmax concentration.
- Unpaired t test was done to see relation between trough plasma concentration of patients with low and high INR with trough concentration of patients with normal INR.
- Similarly unpaired test was done to see relation between Cmax plasma concentration of patients with low and high INR with Cmax concentration of patients with normal INR.
- One way analysis of variance (ANOVA) was used to compare only the trough plasma concentration of acenocoumarol of patients with INR 1.5-4.5 (all the three groups)
- Similarly One way analysis of variance (ANOVA) was used to compare only the Cmax plasma concentration of acenocoumarol of patients with INR 1.5-4.5 (all the three groups).

A P Value of <0.05 was considered statistically significant.

RESULTS

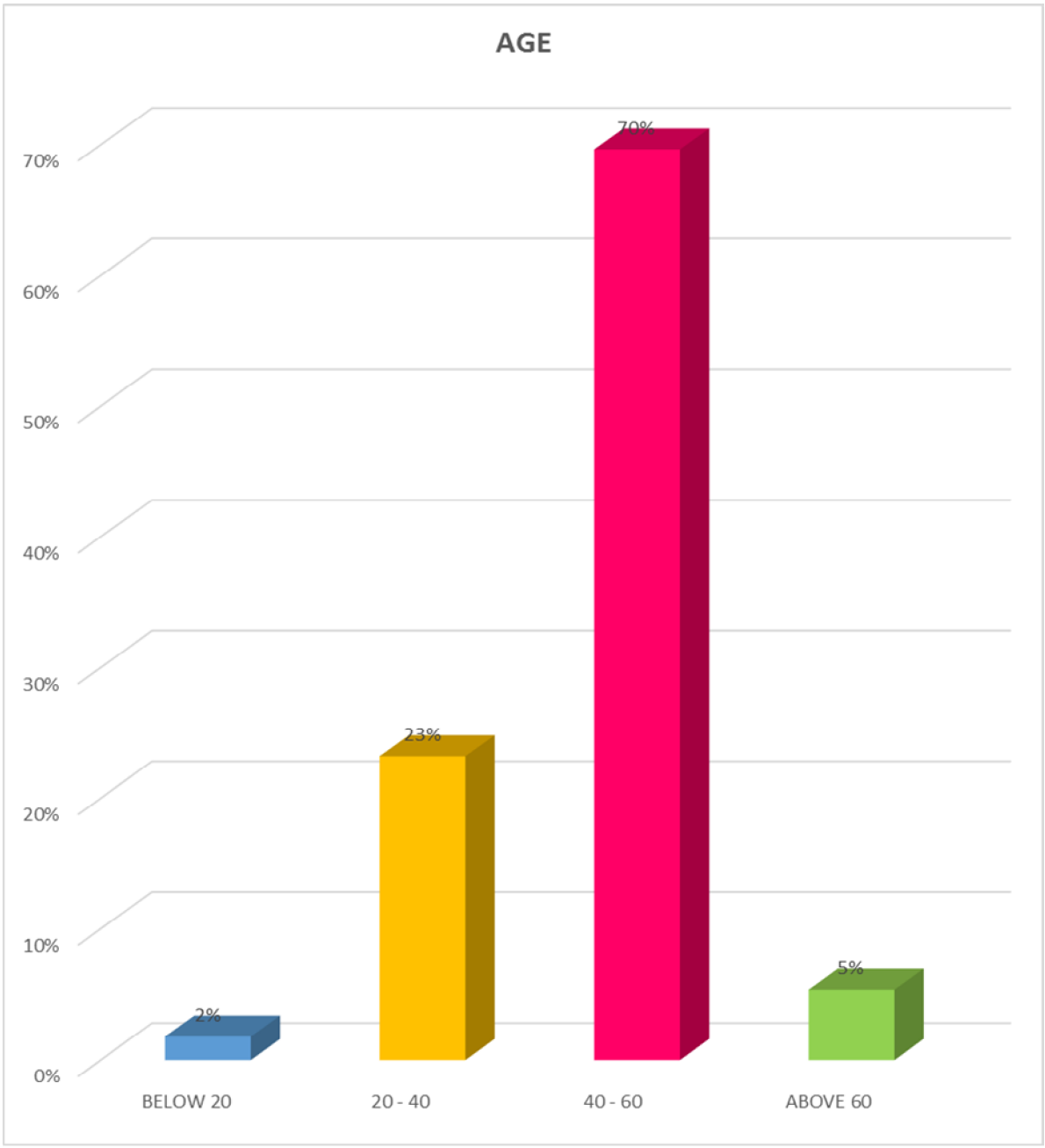
- Total of 56 participants were enrolled
- These participants belongs to three groups of INR.
- One group with low INR and these participants were 15 in number.
- The participants with normal INR were 30 in number.
- While participants with high INR was 11 in number.
- It was found that there no complications or adverse effects in all 56 participants

Fig 1: Distribution of Male and Female among valve replaced participants



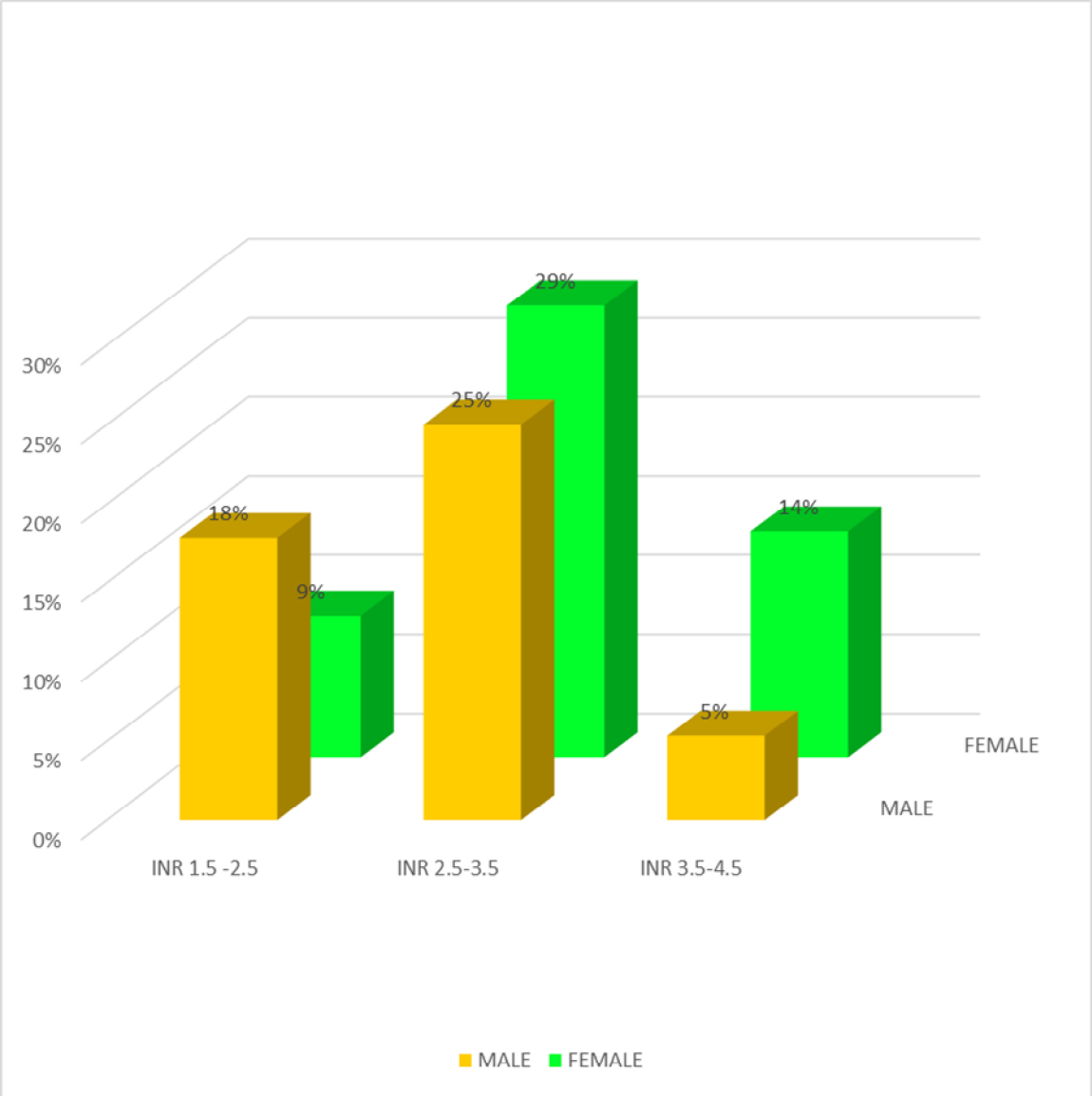
Out of the 56 participants there were equal number of male and female participants. (50% in each group - 28 in each group].

Fig 2: Distribution of the total participants



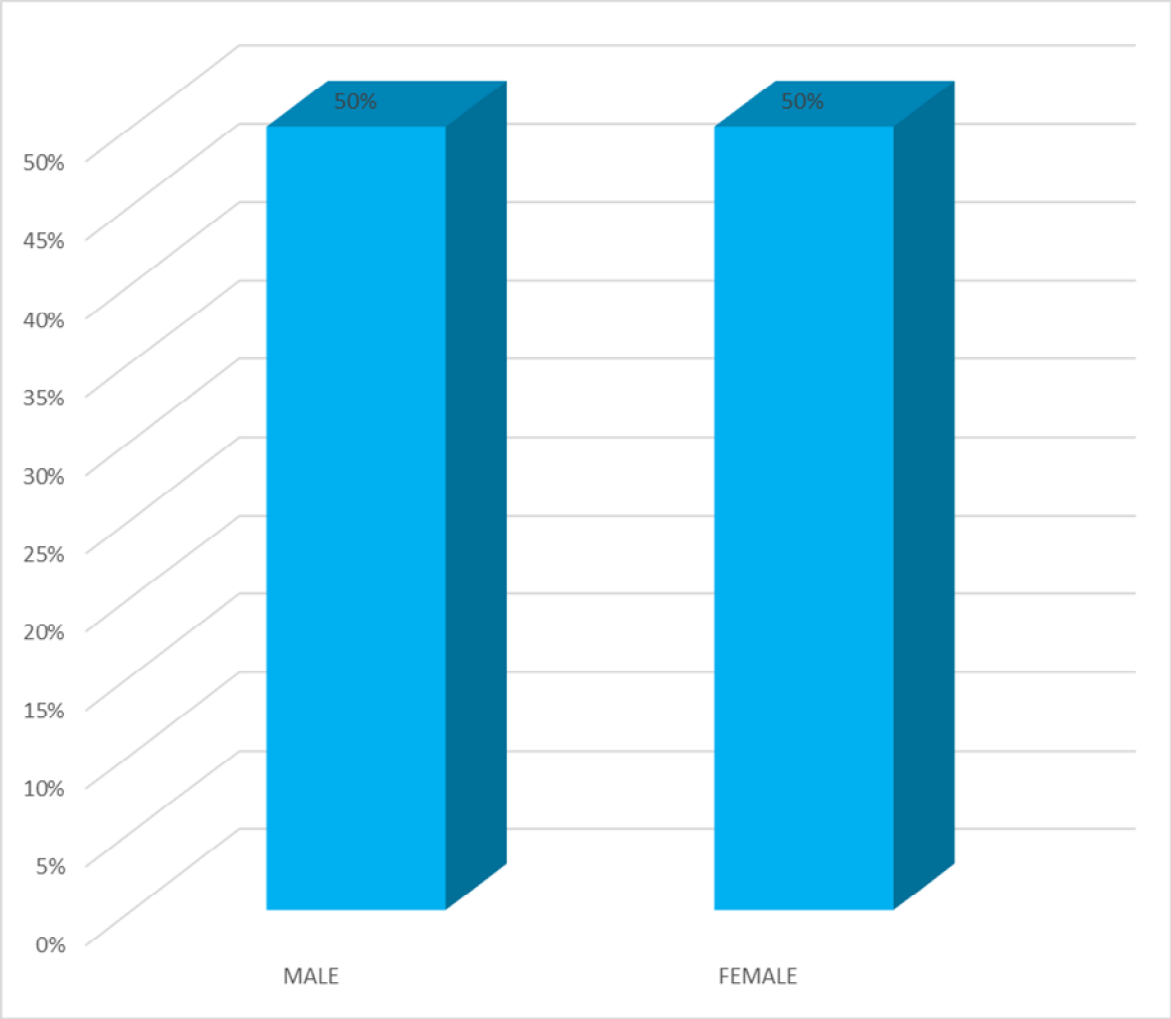
In our study there were more number of participants in age group of 40-60 years. (70%).In the age group of 20-40 years the percentage of participants present were 23%. Above 60 years of age there were about 5% of participants, while below 20 years there were only 2% of participants.

Fig 3: Distribution of male and female patients in INR between 1.5- - 2.5, 2.5 – 3.5 and 3.5 - 4.5



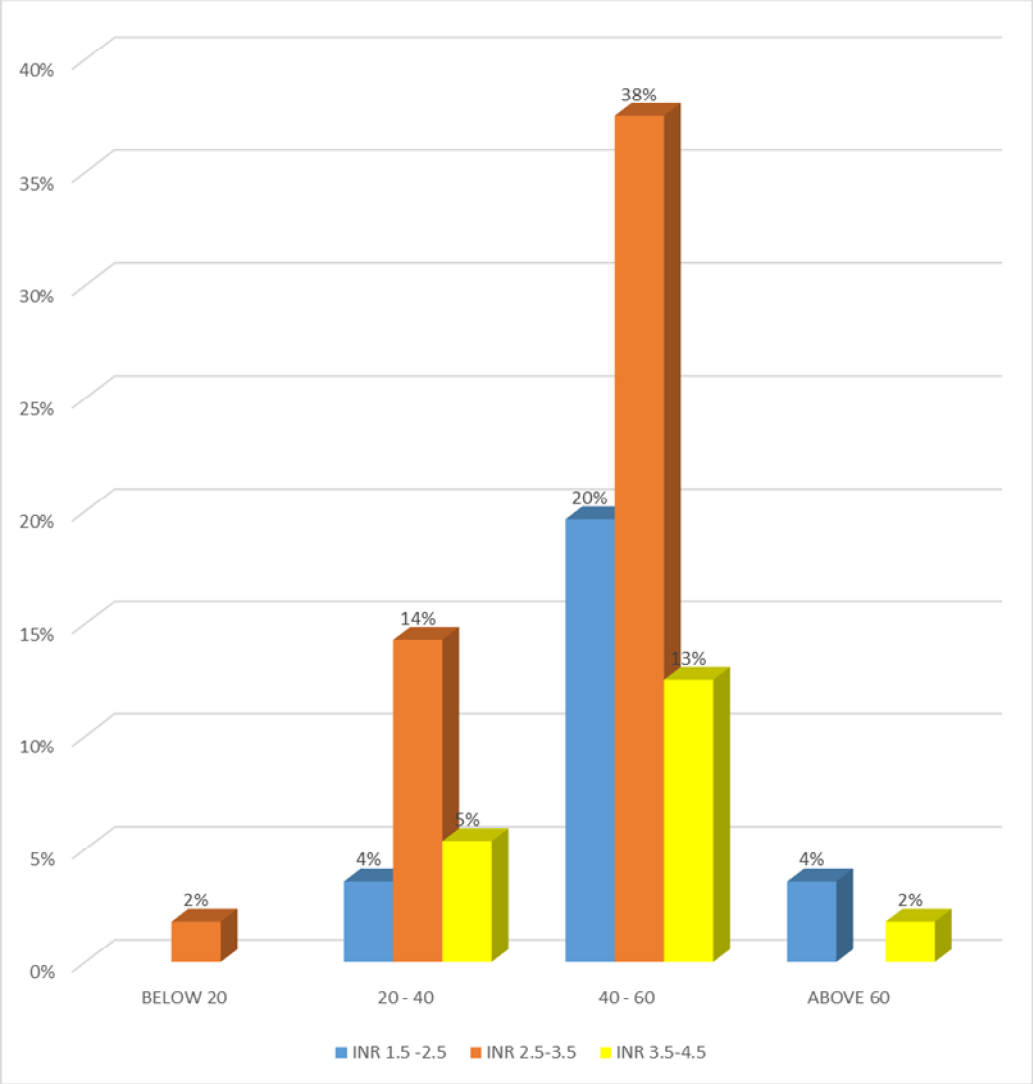
Males were more (15%) in low INR group while females were 9% In participants with INR 1.5 – 2.5 the male were around 18% and the females were 9%. Females were more in normal INR group and high INR group, 29% and 14% respectively while males were 25% and 5% in both groups.

Fig 4: Distribution of sex in poorly controlled INR



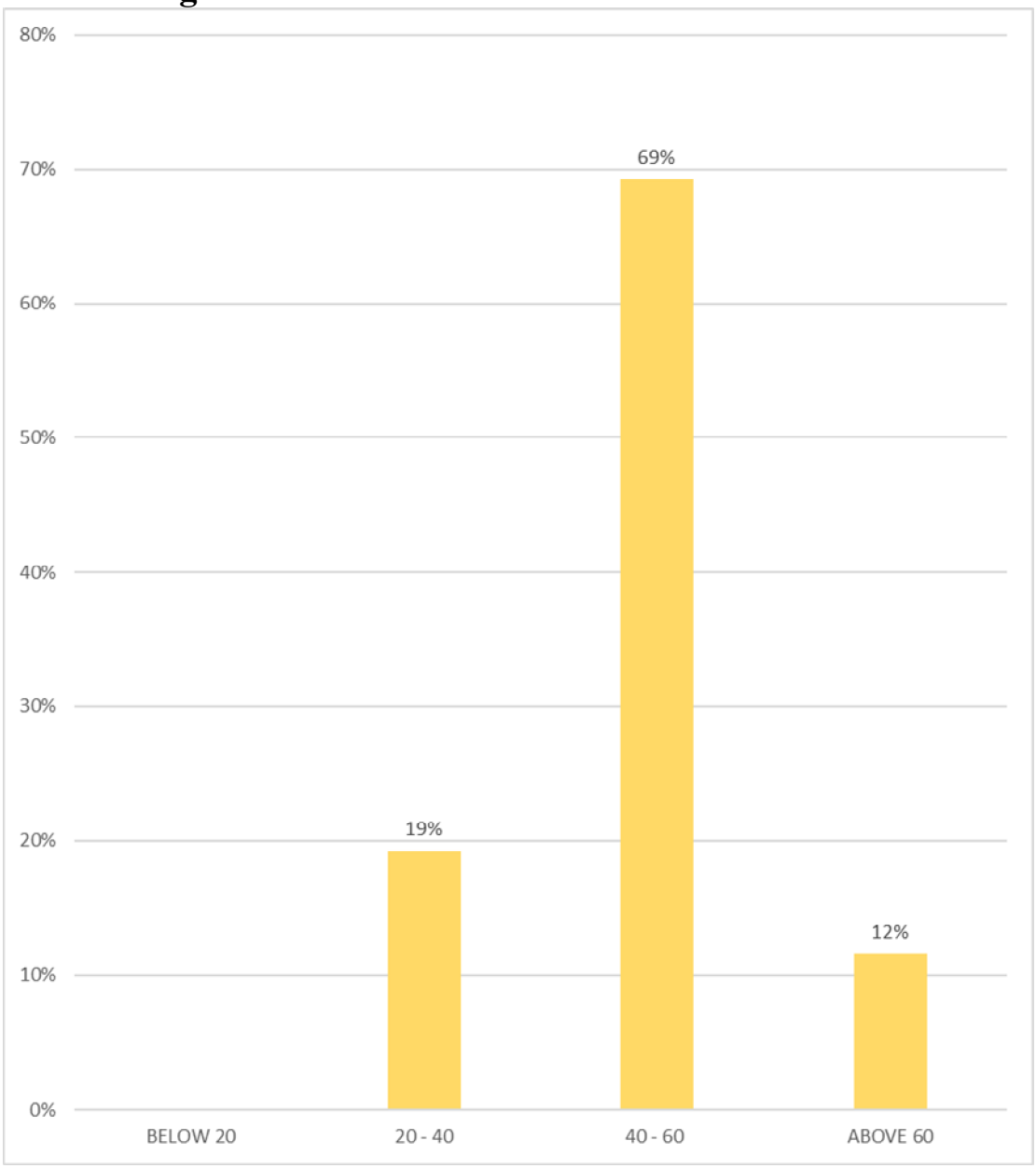
50% of males and females were found in poorly controlled INR group [low INR (1.5-2.5) and high INR group (2.5-3.5)

Fig 5: Distribution of INR between 1.5 – 2.5, 2.5 – 3.5 and 3.5 – 4.5 with reference to age



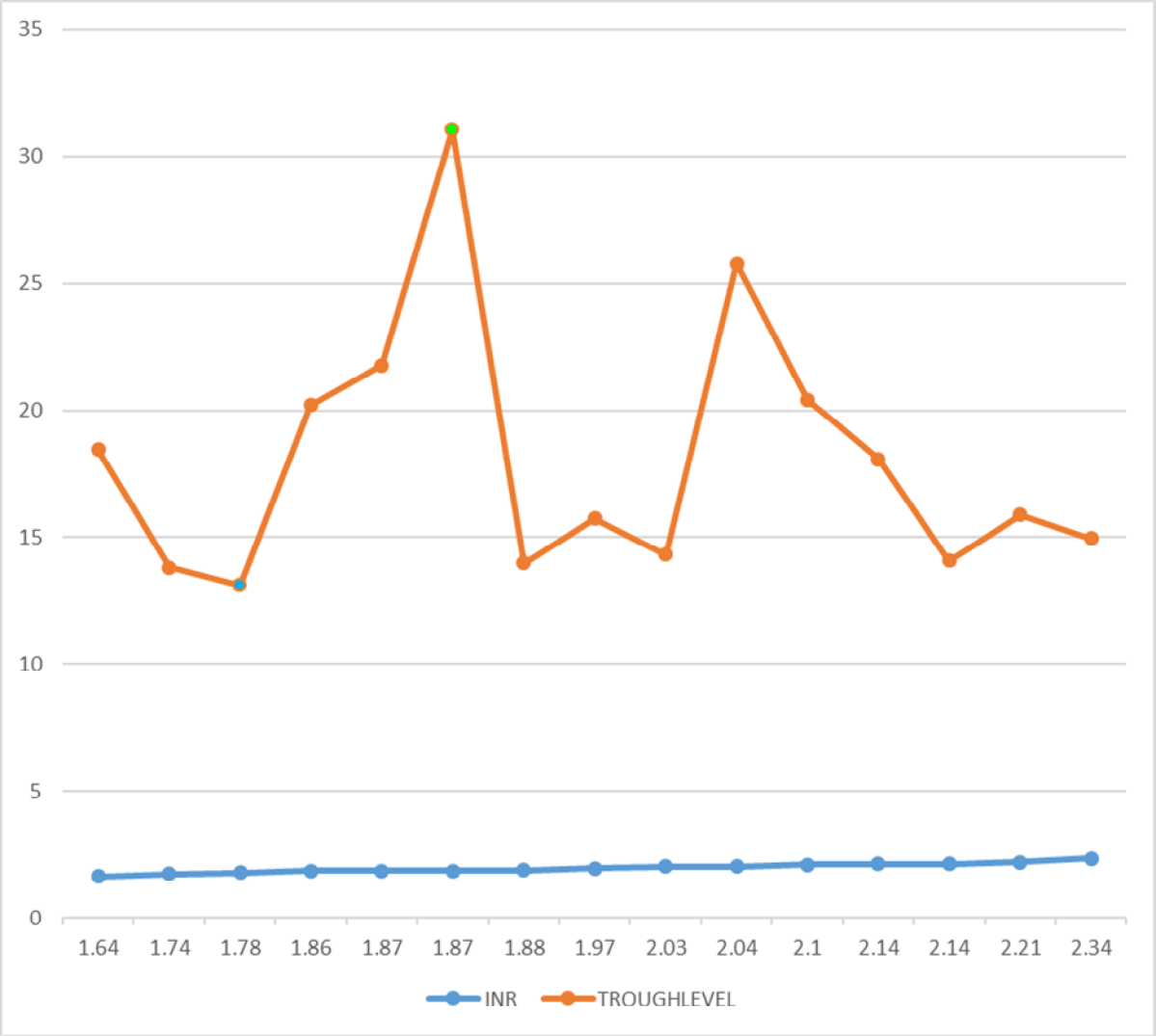
In all the three groups of INR we found that maximum participants were in the age group of 40-60 years while participants with age group 20-40 years were the second highest. Least number of participants were above 60 years and below 20.

Fig 6: Distribution of participants in poorly controlled INR with reference to age



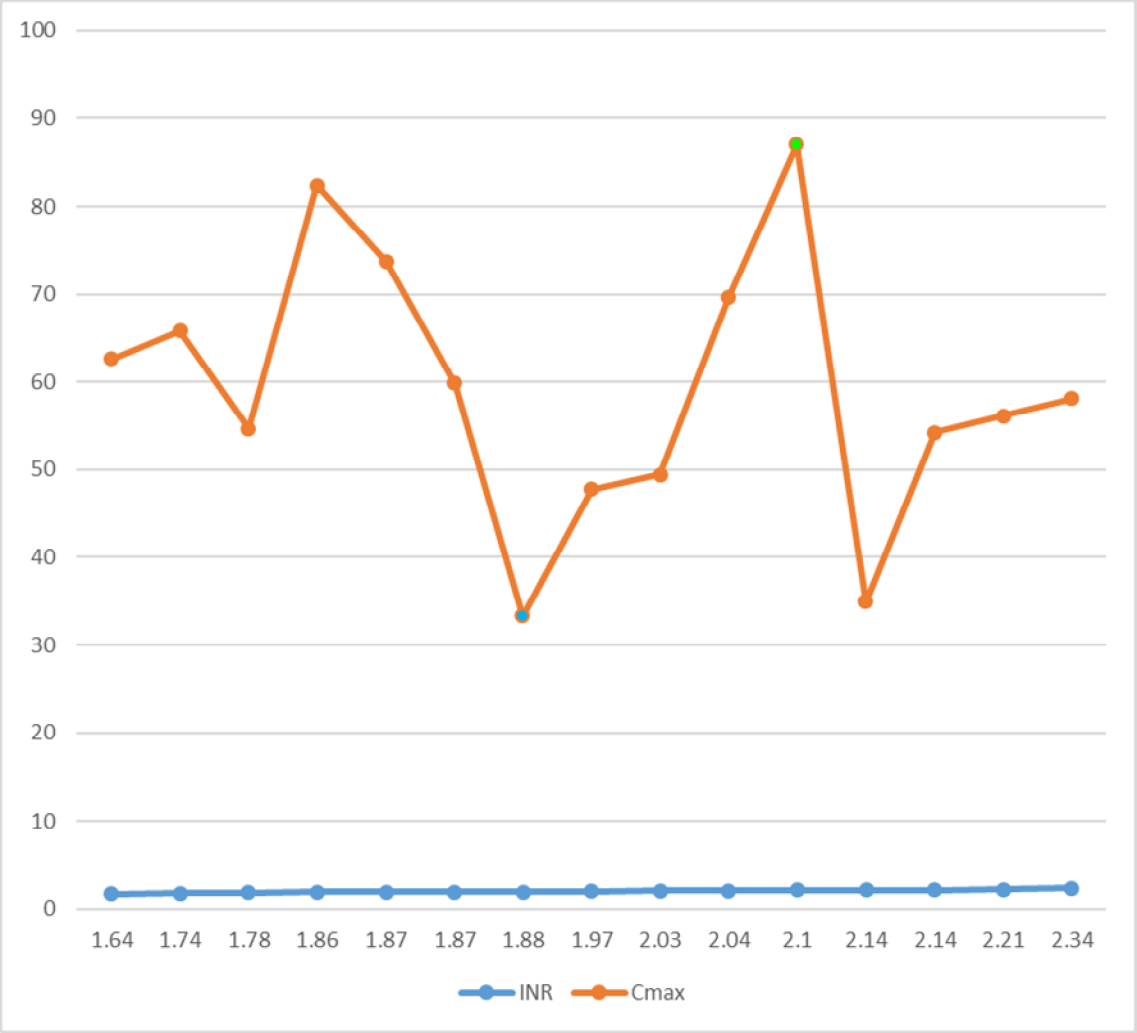
The maximum number participants in poorly controlled INR [low INR (1.5-2.5) and high INR group (2.5-3.5)] belong to the age group 40 – 60 (69%) and 19% of participants were in the age group of 20 – 40 years. In the age group above 60 years 12% of participants were present.

Fig 7: Association between plasma trough concentrations of acenocoumarol (in ng/ml) in participants with INR 1.5 to 2.5



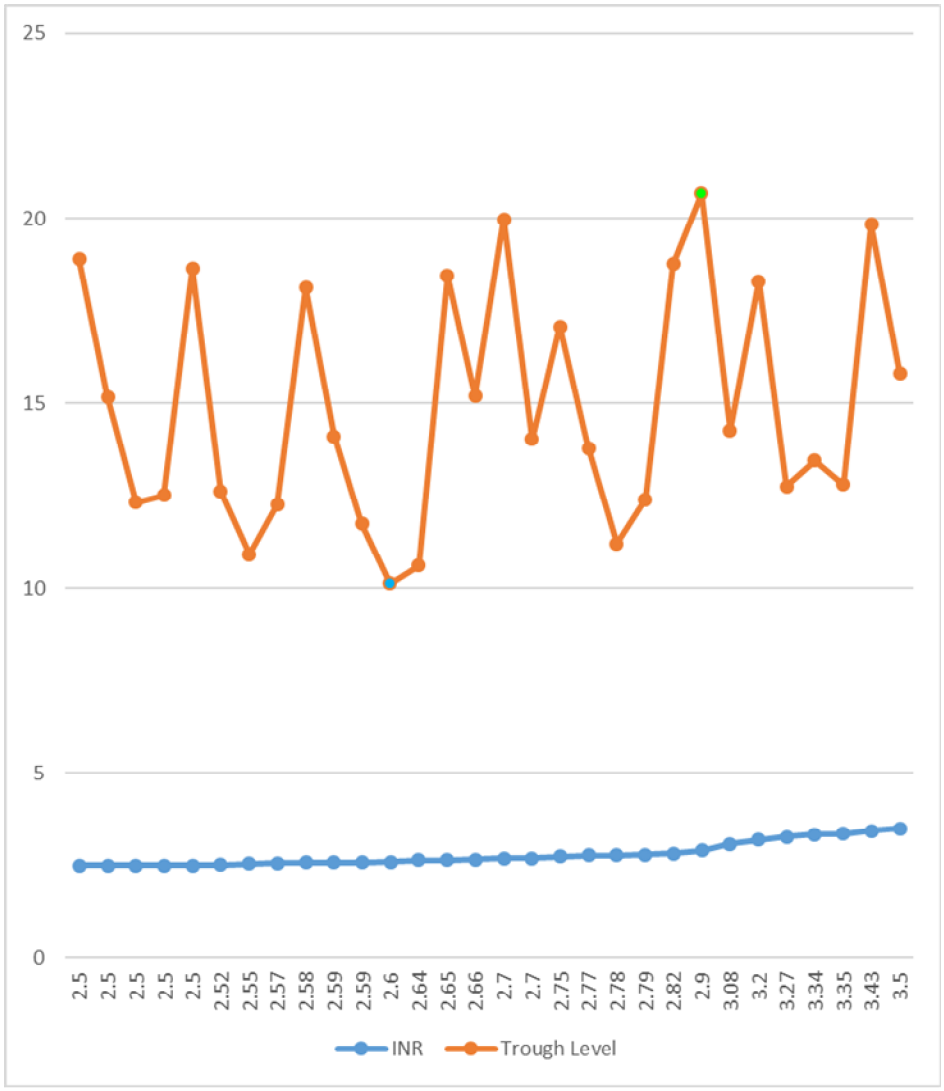
Association between the trough concentration and INR 1.5 to 2.5 was compared. The highest trough concentration of 31ng/ml was in participant with INR 1.87. While the lowest trough concentration of 13ng/ml was seen in participant with INR 1.78.

Fig 8: Association between plasma Cmax concentrations of acenocoumarol (in ng/ml) in participants with INR 1.5 to 2.5



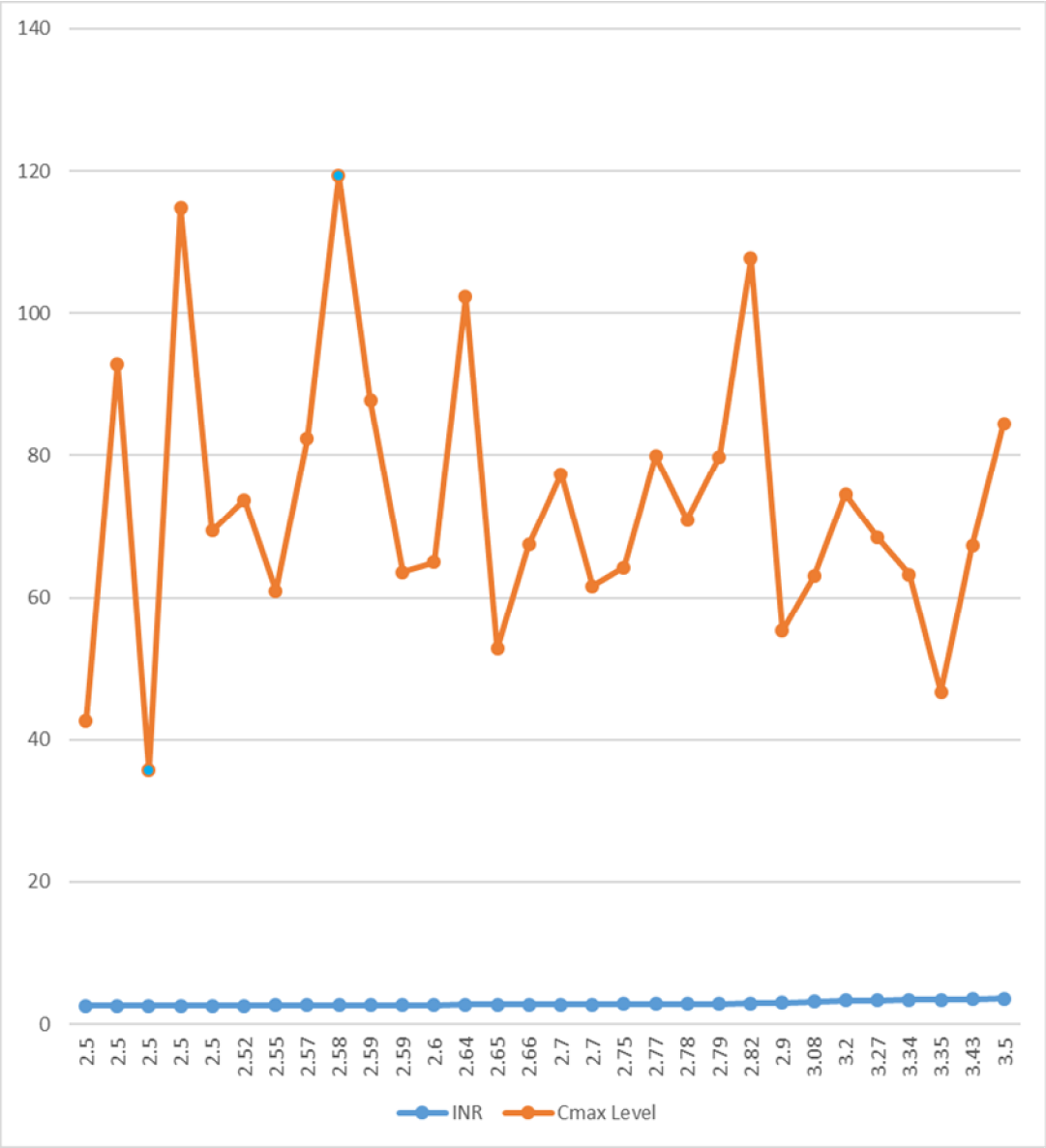
Association between Cmax plasma concentration and INR 1.5-2.5 was analysed. Lowest Cmax concentration was found to be 32ng /ml in participants with INR 1.88 and the maximum Cmax concentration of 88 ng/ml was seen in participants with INR 2.1.

Fig 9: Association between plasma trough concentrations of acenocoumarol (in ng/ml) in participants with INR 2.5 to 3.5



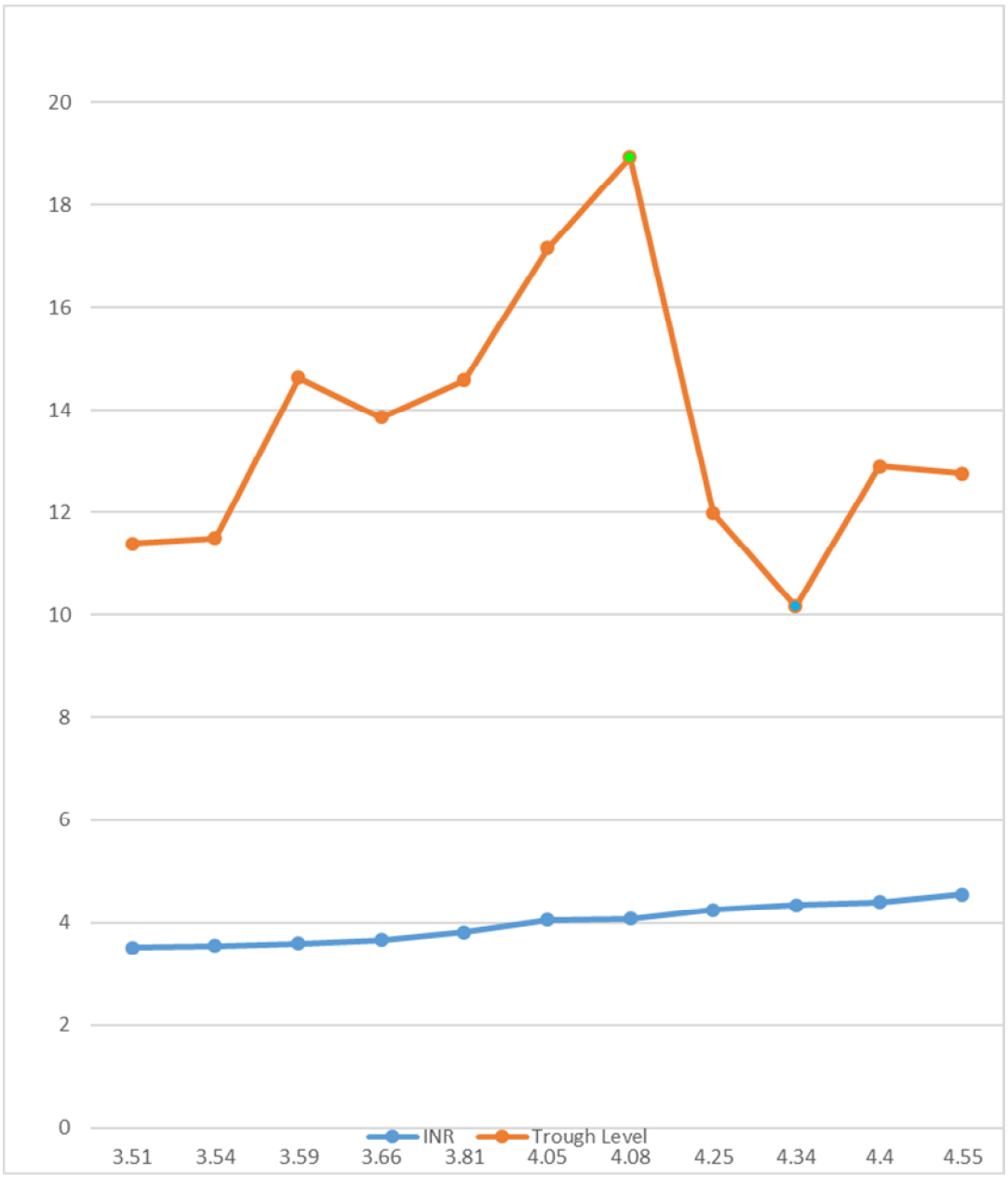
The association between trough concentration and INR 2.5 – 3.5 was analyzed. The highest trough concentration of 22 ng/ml was seen in participants with INR 2.82. While the lowest trough concentration was seen in patient with INR2.6 and concentration was 10ng/ml.

Fig 10: Association between plasma Cmax concentrations of acenocoumarol (in ng/ml) in participants with INR 2.5 to 3.5



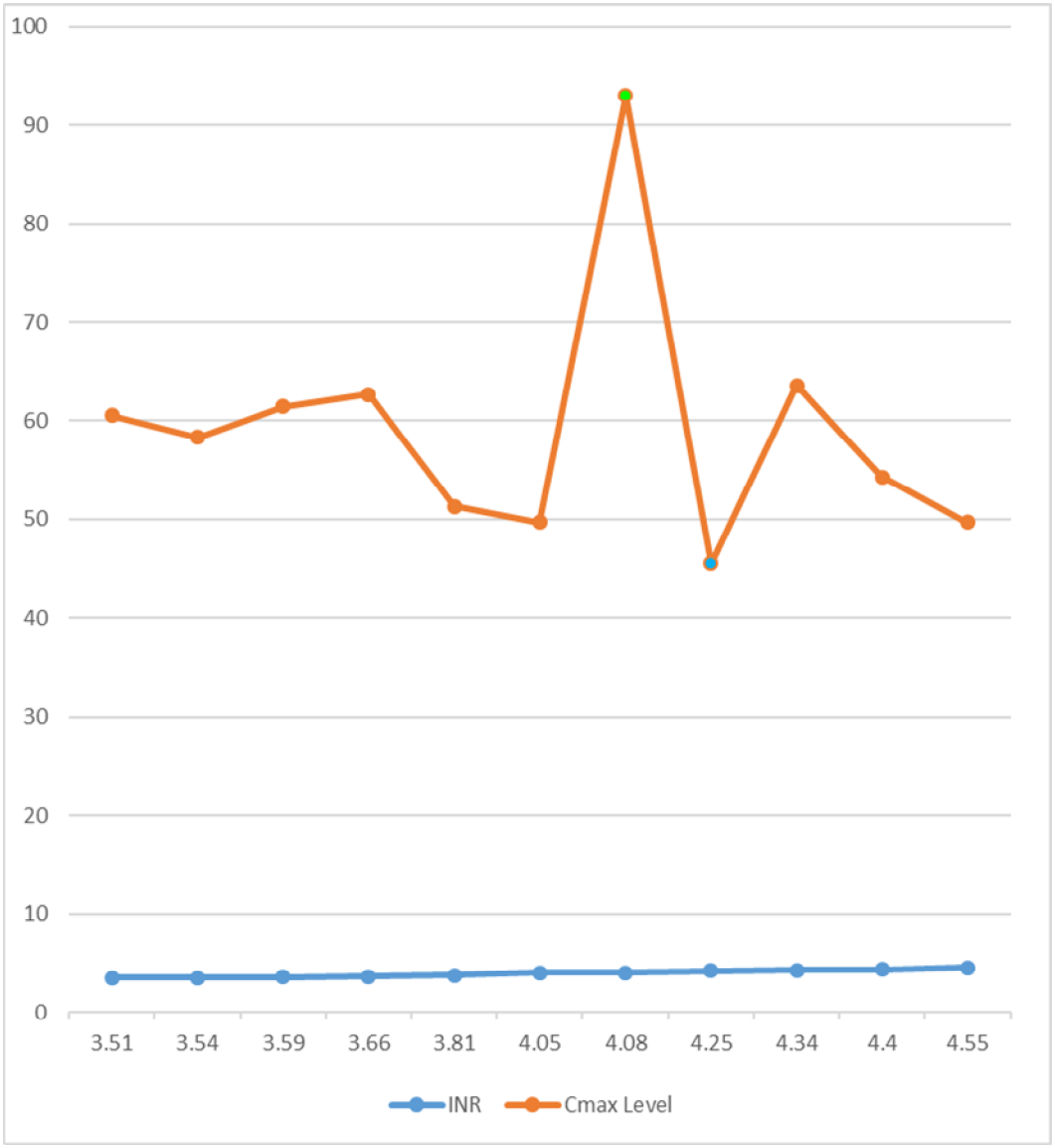
Association between plasma Cmax concentrations of acenocumarol in participants with INR 2.5 - 3.5 was analysed .The maximum Cmax concentration was 120ng/ml while INR was 2.59. While the participant with INR 3.27 had the lowest concentration of 28ng/ml/.

Fig 11: Association between plasma trough concentrations of acenocoumarol (in ng/ml) in participants with INR 3.5 to 4.5



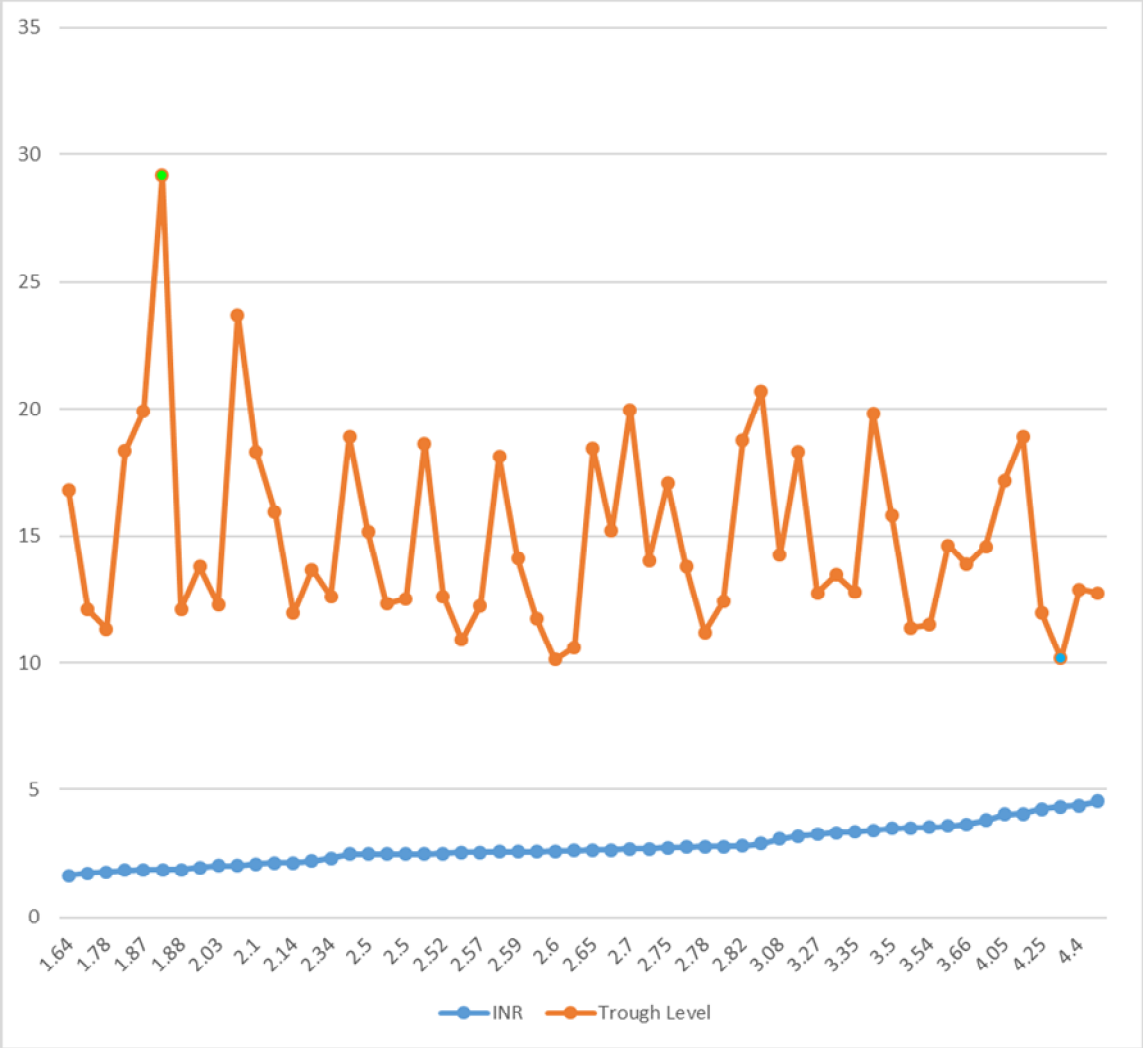
The association between plasma trough level plasma concentration of acenocoumarol and INR 3.5 – 4.5 was analysed. The participant with INR 4.08 had maximum trough concentration of 19ng/ml, while a participant with INR 4.34 had the lowest trough concentration of 10ng/ml.

Fig 12: Association between plasma Cmax concentrations of acenocoumarol (in ng/ml) in participants with INR 3.5 to 4.5



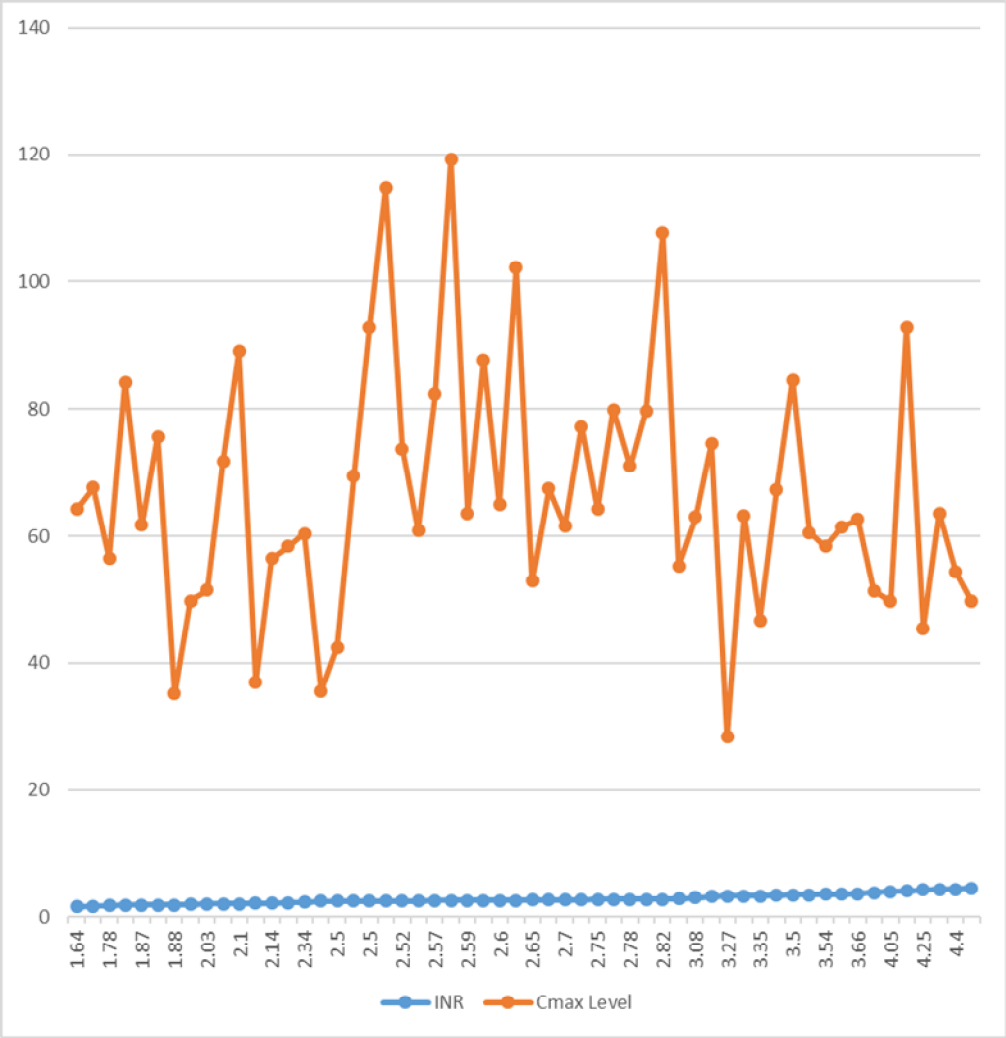
The association between INR and Cmax plasma concentration of acenocoumarol in participants with INR 3.5 – 4.5 was analysed .The lowest Cmax concentration of 45ng/ml was noted with INR 4.25, while the highest Cmax concentration of 92ng/ml was noted with INR 4.08.

Fig 13: Association between plasma trough concentrations of acenocoumarol (in ng/ml) in participants with INR 1.5 to 4.5



The association between INR and trough level plasma concentration of acenocoumarol in participants with INR 1.5 – 4.5 (all the 3 groups) was analysed. The highest trough concentration of 29ng /ml was found in a patient with INR 1.88. The a lowest trough concentration of 10ng/ml was in a participant with INR 4.25.

Fig 14: Association between plasma Cmax concentrations of acenocoumarol (in ng/ml) in participants with INR 1.5 to 4.5

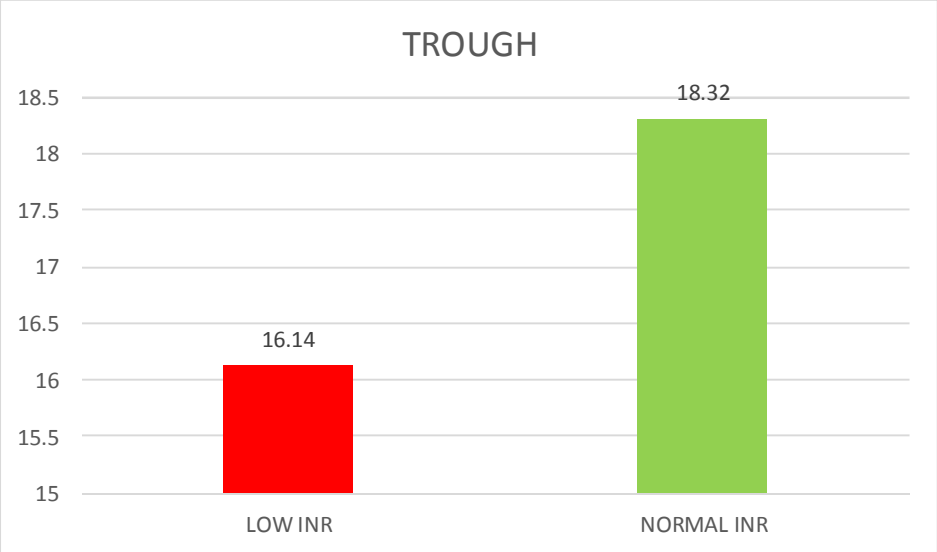


Association between of INR and Cmax level plasma concentration of acenocoumarol in participants with INR 1.5 – 4.5 (all the 3 groups) showed that participant with INR 2.59 had a Cmax concentration of 120ng/ml which was the highest. But a participant with INR 3.27 had 28ng/ml of Cmax concentration which was found to be the lowest.

TABLE 1: MEAN TROUGH AND CMAX CONCENTRATIONS OF ALL THREE GROUPS:

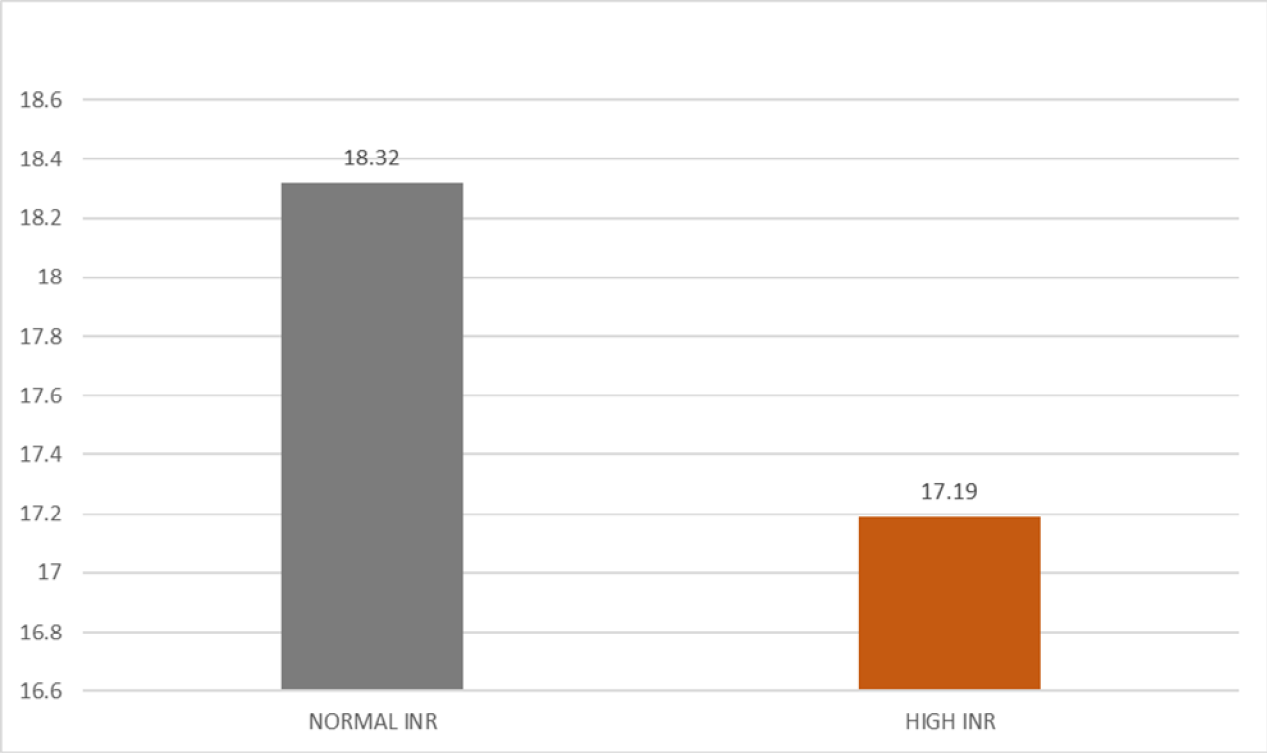
PLASMA CONCENTRATION	PARTICIPANTS WITH INR 1.5-2.5	PARTICIPANTS WITH INR 2.5-3.5	PARTICIPANTS WITH INR 3.5-4.5
MEAN TROUGH CONCENTRATION OF ACENOCOUMAROL in ng/ml	16.14	18.79	17.19
MEAN Cmax CONCENTRATION OF ACENOCOUMAROL in ng/ml	56.3	59.1	57.3

Fig 15: Comparisons of mean plasma trough concentration of acenocoumarol (ng /ml) in participants with INR 1.5 – 2.5 and 2.5 - 3.5



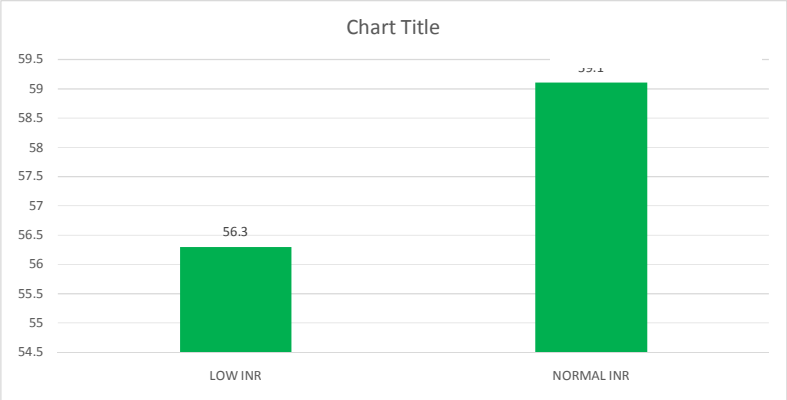
The comparison between mean trough plasma concentration of participants with INR 2.5-3.5 and participants with INR 1.5-2.5 was analysed. The mean trough concentration was 16.14ng/ml with INR 1.5 and 2.5 while 18.32ng/ml was seen with INR 2.5 and 3.5

Fig 16: Comparisons of mean plasma trough concentration of acenocoumarol (ng/ml) in participants with INR 2.5-3.5 and 3.5-4.5



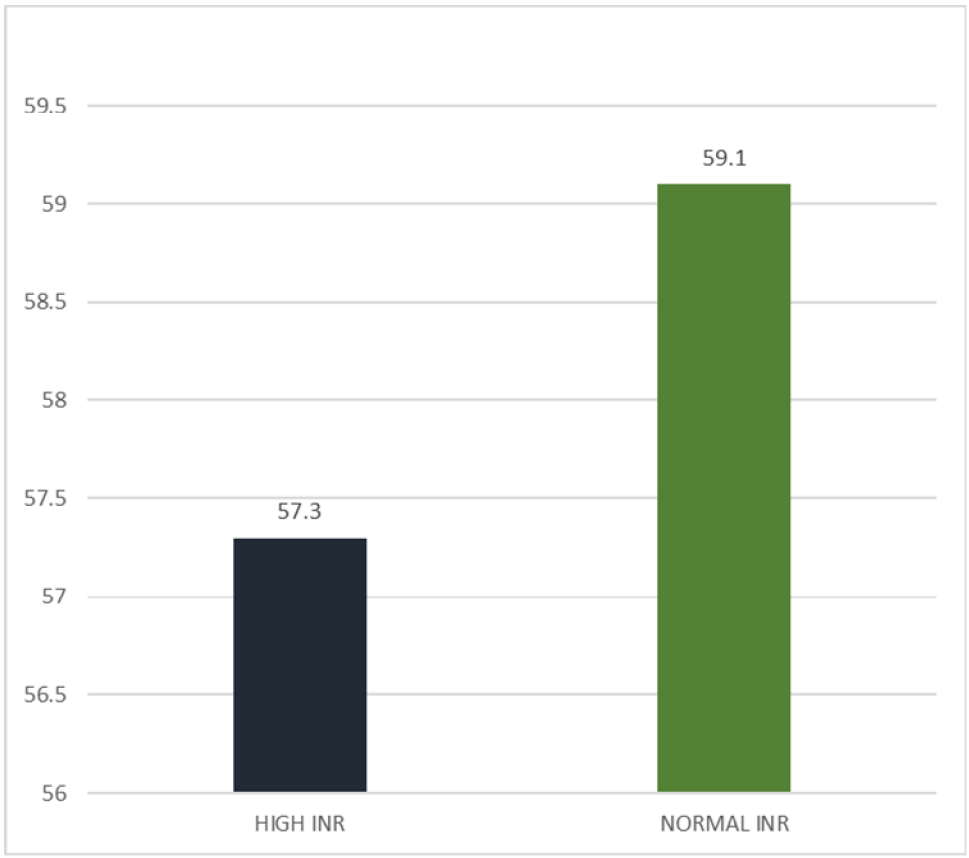
Comparison of mean trough plasma concentration of participants with INR 2.5-3.5 and 3.5-4.5 was done. The mean trough concentration was 17.19ng/ml with INR between 3.5 and 4.5 while 18.32 ng/ml was seen with between INR 2.5 and 3.5

Fig 17 : Comparison of mean plasma Cmax concentration of acenocoumarol (ng/ml) in participants with INR 1.5-2.5 and 2.5-3.5



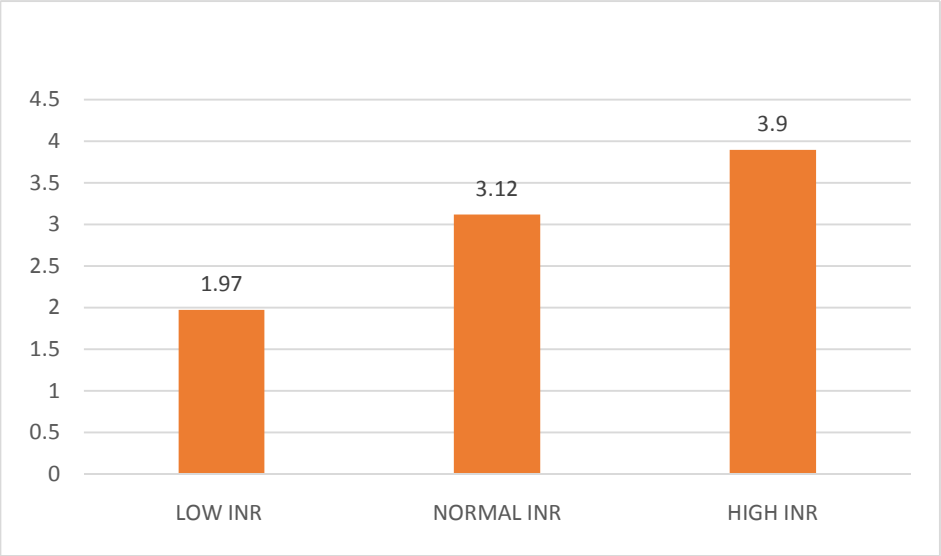
The comparison between mean plasma Cmax concentration of participants with INR 2.5-3.5 and 1.5-2.5 was done, which showed the mean Cmax concentration in both groups was similar.

Fig 18: Comparison of mean plasma Cmax concentration of acenocoumarol (ng/ml) in participants with INR 2.5-3.5 and 3.5-4.5



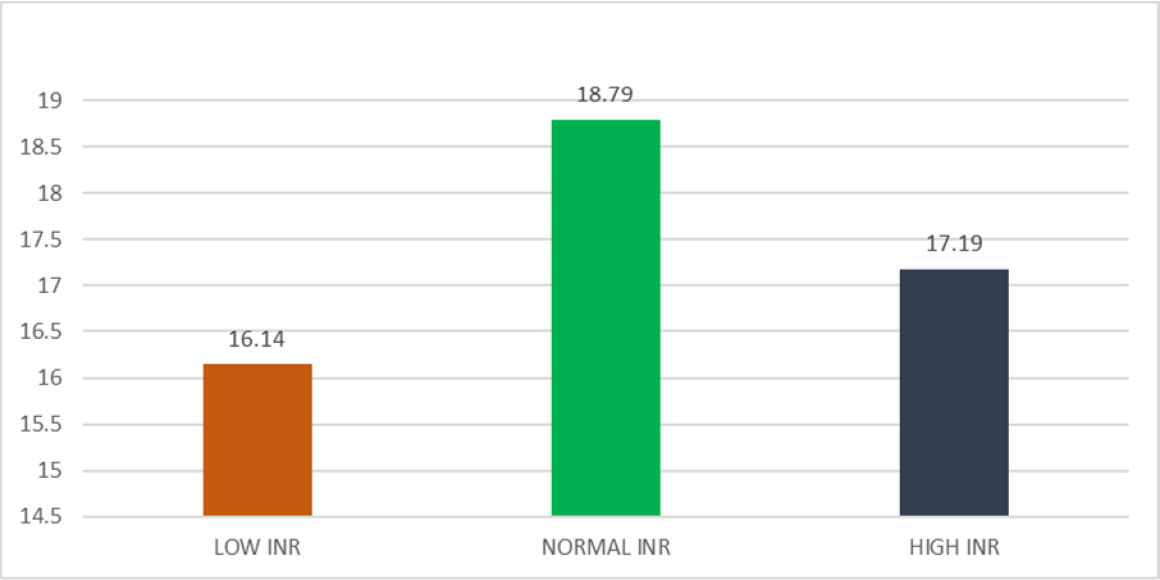
The comparison of mean Cmax of participants with INR 2.5-3.5 and 3.5-4.5 revealed, that Cmax concentration between both the groups was almost the same.

Fig 19: Comparison of mean INR of all groups (low, normal and high)



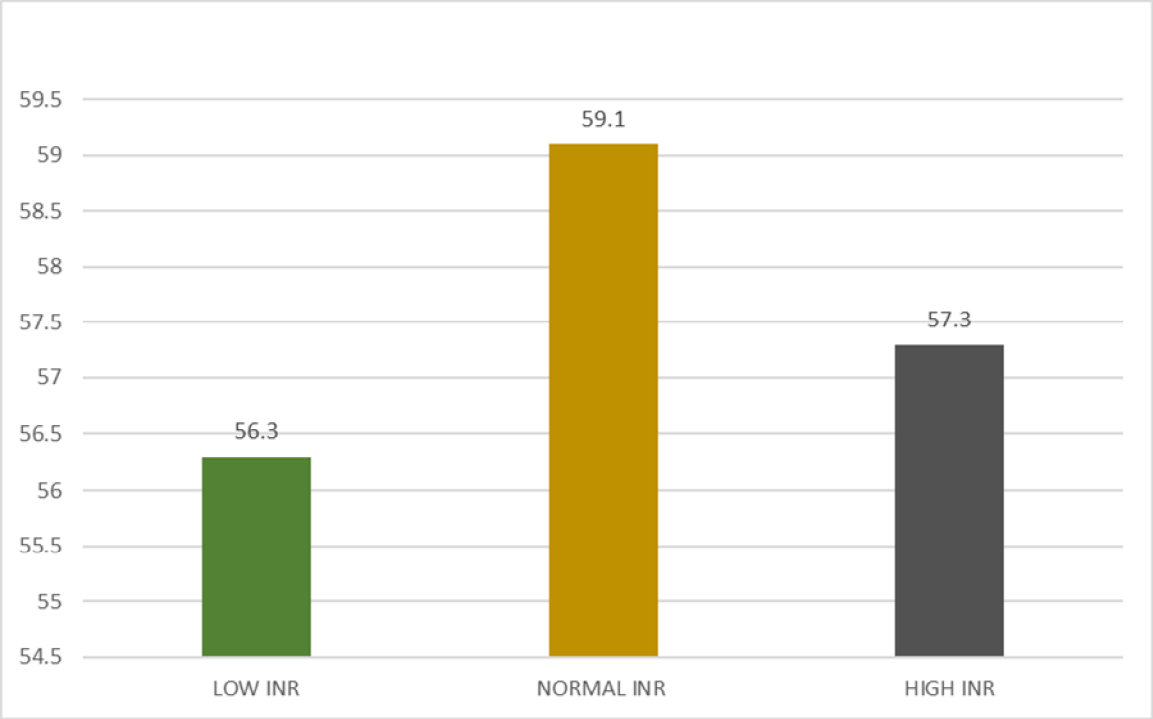
The mean INR of all the three groups (low, normal and high) was compared. The mean INR was 3.9 for High INR group, the mean INR was 3.12 for normal INR group, the mean INR was 1.97 for low INR group.

Fig 20: Comparison of mean plasma trough concentration of acenocoumarol (ng/ml) in participants with INR 1.5-4.5



Only the mean trough concentration of all the three groups (1.5-2.5, 2.5-3.5 &3.5-4.5) was compared and there was no significant difference between three groups.

Fig 21: Comparison of the mean plasma Cmax concentration of acenocoumarol (ng/ml) in participants with INR 1.5-4.5



The mean Cmax plasma concentration of all the groups of participants with INR 1.5-2.5, 2.5-3.5 and 3.5-4.5 was compared and there was no significant difference between three groups

DISCUSSION

Total number of participants for this study was 56. Participants did not found to have any complications or adverse effect due to acenocoumarol . These participants belonged to three groups with different INR. One group with low INR (1.5-2.5) and these participants were 15. The participants with normal INR (2.5-3.5) were 30. While participants with high INR (3.5-4.5) was 11. All these participants were on 2mg of acenocoumarol for at least 3 months, before the sample was collected from them. Blood samples were collected from these participants at the trough and Cmax levels.

Acenocoumarol is the most frequently used oral anticoagulant in valve replaced participants. This drug has a narrow therapeutic index .The most important and serious adverse effect of this drug is profuse bleeding which is life threating. To prevent this complication repeated and frequent estimation of INR is done. There are previous studies which confirms the variation of INR according to the laboratory tested. Studies also proves the inverse relation between INR and dose of the anticoagulant. There are studies which compared the relation between INR and plasma concentration of warfarin. These studies were done in Europe, China and in India [74, 75 76]. All these studies confirm that there is no association between INR and plasma concentration of acenocoumarol .

Our study is the first study to compare INR and plasma concentration acenocoumarol . The aim of our study is to find out the relation between INR and plasma concentration of acenocoumarol . In our study we have compared INR of

three different groups (low, normal and high INR) there plasma concentration taken at trough and Cmax levels respectively. The association between of trough plasma concentration of acenocoumarol with three groups of INR was analyzed. Plasma concentration of acenocoumarol at Cmax of all the three groups of INR was analyzed.

DISTRIBUTION OF MALE AND FEMALE PARTICIPANTS AMONG THE VALVE REPLACED PAITENTS

There were equal number of participants in both the sex .They were 50 % in each group. In another study done in Indonesia participants with rheumatic heart disease, males were more and accounted for 95.2% while female were 4.8%.[69] (Fig 1)

DISTRIBUTION OF VALVE REPLACED PARTICIPANTS IN REFERENCE TO AGE

In our study we had maximum number of participants in age group 40-60 (70%).In the age of 20-40 yrs. the percentage of participants were 23%. Above 60yrs of age we had only 5% of participants. While below 20 yrs, there were only 2 % of participants. There is a study done in Australia which reveals maximum number of participants with rheumatic heart disease between 50.9 –71.4. In our study we have maximum number of participants in age group of 40 – 60 yrs.[70.] (Fig. 2)

DISTRIBUTION OF MALE AND FEMALE PARTICIPANTS IN INR 1.5 – 2.5, 2.5 – 3.5, 3.5 – 4.5.

In RHD patients, males were maximum in participants with INR 1.5 – 2.5. In a study done in South India participants with low INR, female were more in number. But in our study we have more males. In participants with INR 2.5 – 3.5 and 3.5 – 4.5 there were more females and they were 29% and 14% in each group respectively. While the participants with INR 2.5 – 3.5 there were 25% males. But in INR 3.5 – 4.5 group males were only 5%.(Fig. 3)

In a study done in Netherlands, participants with INR between 2.5 – 3.5 and another group with INR 3 – 4 were taken. In these groups the number of males and females participants were 107 and 121 respectively. Like our study, the study done in Netherlands also had more female participants.[72]

DISTRIBUTION OF MALE AND FEMALE PARTICIPANTS IN POORLY CONTROLLED INR (INR 1.5-2.5 & INR 3.5-4.5)

In comparing the male and female ratio in participants with poorly controlled INR 1.5 – 2.5 and 3.5 – 4.5 there were equal number in both (50 %).Similar to this study, a study done in India showed participants who were receiving the maximum dose of acenocoumarol > 4mg with low INR were females and another group which was receiving low dose of acenocoumarol with high INR group were females But we had equal number of males and females with poorly controlled INR.(Fg.4)

DISTRIBUTION OF INR BETWEEN 1.5 – 2.5, 2.5 – 3.5 AND 3.5 – 4.5 IN REFERENCE TO AGE

In all three groups of INR the maximum number of participants were in the age group 40 – 60 yrs. while the participants in age group of 20 – 40 years were the next highest.

According to a study done on RHD patients in India, more number of participants were in the age group of 30 – 45yrs with 43.68%. While the next highest was in the age group with 25.29% .But in our study we had more participants in age group of 40 – 60yrs.[73.] (Fig. 5)

DISTRIBUTION OF PAITENTS IN POORLY CONTROLLED INR IN REFERENCE TO AGE

There were more participants in the age group of 40 – 60yrs (69%). 9% of participants were in the age group of 20 – 40yrs and above 60 years of participants were only 12% (Fig. 6)

COMPARISON OF INR ALL THREE GROUPS (LOW, NORMAL AND HIGH) WITH THEIR RESPECTIVE TROUGH CONCENTRATION OF ACENOCOUMAROL

The INR (low, normal, high) of each was compared with their respective trough plasma concentration. Each comparison revealed that there is no significant correlation between INR and the respective trough concentrations. (P value >0.05) (Fig 7, 9 11).

Similarly comparison of total INR (1.5-4.5) with trough concentration also showed that is no significant correlation between INR and the trough concentrations of acenocoumarol . (P value >0.05) (Fig13).

COMPARISON OF INR IN ALL THREE GROUPS (LOW, NORMAL AND HIGH) WITH THEIR RESPECTIVE Cmax CONCENTRATION OF ACENOCOUMAROL

The INR (low, normal, high) of each was compared with their respective Cmax plasma concentration. Each comparison revealed that there is no significant correlation between INR and the respective trough concentrations. (P value >0.05) (Fig 8, 10, 12).

Similarly comparison of total INR (1.5-4.5) with Cmax concentration plasma concentration of acenocoumarol also showed that there is no correlation between INR and the trough concentrations of acenocoumarol . (P value >0.05)

Similar to our study there are studies showing the poor correlation between INR and plasma warfarin concentration.. They have found that there is no association between INR and plasma concentration of warfarin. They have discussed that concomitant medications, diet variations, seasonal changes and finally age are the factors which makes INR poorly dependent on plasma warfarin concentration.[74]

From these observations it shows that there is no need to alter the dose of acenocoumarol based on INR, since the concentration is similar

Another study done in Ethiopia, also explained that there was less association between plasma warfarin concentration and INR. They explained that numerous factors and inter-individual differences such as interaction with other drugs, resistance, diet, differing drug metabolisms, Vitamin K status, and other factors are the reasons for low cassociation. (Osman et al. 2005).[81]

A study done in China also proved the poor correlation between INR and plasma concentration of warfarin. All the above studies were done in different geographical location.[75]

A study done in Jipmer (South India) had concluded that participants with INR 2 – 3.5 had no correlation between INR and plasma warfarin concentration. They have also said that warfarin has interindividual variation which makes the dosing problematic. Because of this interindividual variation some participants are sensitive to warfarin, and will require low dose of warfarin. Those participants who are resistant to warfarin .Therefore they will require a higher dose. [76] Warfarin plasma concentration measurement may be helpful in managing participants, especially those participants with fluctuant INR and was those to manage.[74, 75, 76, 81]

All the above studies have the same conclusion as our study, which strengthens the concept that INR measurement alone would be only of limited value for dose-adjustment in participants with complicated situations. There is a need for monitoring of plasma concentration before dose adjustment

COMPARISION OF TROUGH PLASMA CONCENTRATION OF ACENOCOUMAROL IN PARTICIPANTS IN LOW AND HIGH INR GROUP WITH THE TROUGH CONCENTRATION OF PARTICIPANTS WITH NORMAL INR

Mean trough plasma concentration of acenocoumarol of low and high INR group with the mean trough concentration of participants with normal INR were compared. There was no significant difference between trough concentrations of different groups it was all most similar as the P value > 0.05.(Fig 15,16 and Table 1)

COMPARISION OF MEAN Cmax PLASMA CONCENTRATION OF ACENOCOUMAROL IN PARTICIPANTS IN LOW AND HIGH INR GROUP WITH THE Cmax CONCENTRATION OF PARTICIPANTS WITH NORMAL INR

Mean Cmax concentration of low and high INR group with the mean Cmax concentration of participants with normal INR were compared. There was no significant difference beween the comparisons showed it was similar as the P value > 0.05.(Fig 15,16 and Table 1)

COMPARISION OF MEAN INR OF THREE GROUPS

The mean INR of all the three groups (low, normal and high) was compared. The mean INR was 3.9 for High INR group, the mean INR was 3.12 for normal INR group, the mean INR was 1.97 for low INR group. (Fig 19)

COMPARISION OF PLASMA MEAN TROUGH CONCENTRATION OF ACENOCOUMAROL IN PARTICIPANTS WITH INR 1.5 – 4.5

Comparison of the plasma trough concentration of all the three group of INR (low, normal and high) was done. Even though these participants belong to various group of INR the trough level was almost similar. The participants with INR 1.5 – 2.5, 2.5 – 3.5 and 3.5 – 4.5, had trough level as 16.14 ng/ml,18.79ng/ml,17.19ng/ml respectively.

The plasma trough concentration of all the three groups is similar as the P value is > 0.05 (Fig 20 and Table 1)

COMPARISION OF PLASMA MEAN C_max CONCENTRATION OF ACENOCOUMAROL IN PARTICIPANTS WITH INR 1.5 – 4.5

Participants with INR 1.5 – 2.5, 2.5 – 3.5 and 3.5 – 4.5 had C_max level as 56.3ng/ml,59.1ng/ml,57.3ng/ml respectively.

The mean C_max of all the three group with different INR did not show any variation, they were almost similar. The plasma mean Cmax concentration of all the three groups is similar as the P value > 0.05.(Fig 21 and Table 1)

Vitamin K antagonists are effective oral anticoagulants drug in preventing and treatment of thromboembolic disease. These drugs have a narrow therapeutic range and shows inter and intra individual variability in dose requirement which is largely determined by both environmental and genetic factors. With the use

of oral anticoagulant the dose response relationships are unpredictable.

So it is difficult to predict maintenance dose for acenocoumarol which varies from 1mg to 56mg.[79] The large variation in dose requirement is influenced mainly by pharmacokinetic and pharmacodynamics features.[80]In routine practice the dose adjustment for acenocoumarol is done by INR monitoring with acenocoumarol . But studies carried out in four different zones in the world have concluded that there is poor correlation between INR and plasma warfarin concentration. [74 75 76 81]

Now in our study we have found a similar finding for acenocoumarol .We have found that there is no correlation between INR of three groups and plasma concentration of acenocoumarol . (Trough & Cmax)

Monitoring INR alone, will have limited value for dose adjustment of acenocoumarol as proved by other studies. The plasma concentration estimation of warfarin will be more appropriate for dose adjustments.

We have also found that there is no significant difference in plasma concentration in all three different group of INR 1.5 – 2.5, 2.5 – 3.5 and 3.5 – 4.5.Which also confirms INR may not a reliable and appropriate marker for the adjusting dose of acenocoumarol .

So the measurement of acenocoumorol in plasma will be more accurate, precise and reliable method for the dose adjustment in patients compared to INR

CONCLUSION

1. This is the first study to compare INR with plasma concentration of acenocoumarol taken at trough and Cmax level.
2. There was no correlation between INR and plasma concentration of aceno-coumarol taken at trough and Cmax level for all the three groups
3. There was no significant difference between mean trough concentrations between three groups of INR
4. There was no significant difference between mean Cmax concentrations between three groups of INR
5. Therefore we can conclude that measuring INR alone, will have limited value for dose adjustment of acenocoumarol as proved by other studies for warfarin
6. Hence estimation of plasma concentration of acenocoumarol will be ideal and appropriate for the dose adjustment of acenocoumarol .
7. However the findings of this study has to be further confirmed with larger sample size for extremes of INR.

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Annexure 1

Major systemic illness causing coagulation disturbance

Congenital:

- Hemophilia
- Factor 5 Leiden mutation
- Protein C deficiency
- Protein S deficiency
- Von Willebrand's disease (vWD)

Acquired:

- Liver disease and cirrhosis
- Shock
- Sepsis
- Malignancy
- Renal disease
- Prolonged steroid use
- Anti-phospholipid antibody syndrome (APLAS)
- Systemic Lupus Erythematosus (SLE)

Annexure 2

Drugs Interactions with acenocoumarol

- Allopurinol
- Amiodarone
- Azathioprine
- Betamethasone
- Carbamazepine
- Cefoxitin
- Cholestyramine
- Cimetidine
- Dexmethasone
- Doxycycline
- Erythromycin
- Fenofibrate
- Fluvostatin
- Gingko biloba
- Ibuprofen
- Ketoconazole
- Lovastatin
- Orlistat
- Quinine
- Zafirlukast

ABBREVATIONS

Rheumatic heart disease – RHD

International Normalized Ratio - INR

Oral anticoagulation - OAC

Vitamin K antagonists - VKA

Thromboembolic events - TE

Therapeutic drug monitoring –TDM

High –performance liquid chromatography – HPLC

Nano grams per millilitre – ng/ml

PSG Institute of Medical Science and Research, Coimbatore
Institutional Human Ethics Committee
INFORMED CONSENT FORMAT FOR RESEARCH PROJECTS

I, , **Dr. D. Jeyalakshmi** am carrying out a study on the topic: COMPRATIVE STUDY ON ESTIMATION OF ACENOCOUMAROL LEVELS IN BLOOD IN PATIENTS WITH EXTREMES OF INR VALUES AND NORMAL INR VALUES AFTER VALVE REPLACEMENT SURGERY as part of my research project being carried out under the aegis of the Department of PHARMACOLOGY.

My research guide is: Dr.S. Bhuvaneshwari, MD., Professor of the department, Pharmacology.

The justification for this study is: This study will be helpful in predicting optimal acenocoumarol dose requirements. This study identifies patients at increased risk of supra-therapeutic INR (International Normalized Ratio) values and cerebrovascular bleeding events. This allows personalization of dosing and to prevent cerebrovascular bleeding events

The objectives of this study are

- . Selecting patients with normal INR [2.5-3.5] and extremes INR [1.5-2.5 and 3.5-4.5] after valve replacement surgery estimating acenocoumarol in blood.
- Comparing levels of acenocoumarol in blood in patients with normal INR and patients with extremes of INR.

Sample size: 60

Study volunteers / participants are (specify population group & age group): Patients with INR 1.5 to 4.5 and who have undergone mechanical heart valve replacement surgery at PSG Hospitals, Coimbatore, India

Location: The study will be conducted in the Department of Cardiothoracic & Vascular Surgery, PSG Hospitals, and Coimbatore, India

We request you to kindly cooperate with us in this study. We propose collect background information and other relevant details related to this study. We will be carrying out:

Initial interview (specify approximate duration): 10 minutes.

Health education sessions: Nil

Clinical examination (Specify details and purpose): Nil

Data collected will be stored for a period of five years. We will not use the data as part of another study.

Blood sample collection: Specify quantity of blood being drawn: 4 ml.

No. of times it will be collected: 2

Whether blood sample collection is part of routine procedure or for research (study) purpose:

Research purpose

Specify **purpose**, discomfort likely to be felt and side effects, if any: Pain while pricking

Whether blood sample collected will be stored after study period: No, it will be destroyed

Whether blood sample collected will be sold: No

Whether blood sample collected will be shared with persons from another institution: No

Medication given, if any, duration, side effects, purpose, benefits: Nil

Benefits from this study: This study will be helpful in predicting optimal acenocoumarol dose requirements. This study identifies patients at increased risk of supratherapeutic INR (International Normalized Ratio) values and cerebrovascular bleeding events. This allows personalization of dosing and to prevent cerebrovascular bleeding events.

Risks involved by participating in this study: No risks

How the **results** will be used: **Clinical Meeting at PSG Hospitals**
Dr.MGR Medical University dissertation

If you are uncomfortable in answering any of our questions during the course of the interview / biological sample collection, **you have the right to withdraw from the interview / study at anytime.** You have the freedom to withdraw from the study at any point of time. Kindly be assured that your refusal to participate or withdrawal at any stage, if you so decide, will not result in any form of compromise or discrimination in the services offered nor would it attract any penalty. You will continue to have access to the regular services offered to a patient. You will **NOT** be paid any remuneration for the time you spend with us for this interview / study. The information provided by you will be kept in strict confidence. Under no circumstances shall we reveal the identity of the respondent or their families to anyone. The information that we collect shall be used for approved research purposes only. You will be informed about any significant new findings - including adverse events, if any, – whether directly related to you or to other participants of this study, developed during the course of this research which may relate to your willingness to continue participation.

Consent: The above information regarding the study, has been read by me/ read to me, and has been explained to me by the investigator/s. Having understood the same, I hereby give my consent to them to interview me. I am affixing my signature / left thumb impression to indicate my consent and willingness to participate in this study (i.e., willingly abide by the project requirements).

Signature / Left thumb impression of the Study Volunteer / Legal Representative:

Signature of the Interviewer with date:

Witness:

Contact number of PI: 9566611668
Contact number of Ethics Committee Office: 0422 2570170 Extn: 5818

ஒப்புதல் படிவம்

தேதி :

டாக்டர் D. ஜெயலெட்சுமி ஆகிய நான் , P.S.G மருத்துவக் கல்லூரியின் பார்மகாலஜி துறையின் கீழ் , இருதயவால்வு மாற்று அறுவை சிகிச்சை செய்தவர்களின் ஐ.என்.ஆர் அளவு சராசரி அளவைவிட அதிகம் அல்லது குறைவாக உள்ள நோயாளிகளின் இரத்தத்தின் அசெனொகொமரால் அளவை பரிசோதனை செய்தல் என்ற தலைப்பில் ஆய்வு மேற்கொள்ள உள்ளேன்.

என் ஆய்வு வழிகாட்டி : டாக்டர் . S.புவனேஸ்வரி MD

ஆய்வு மேற்கொள்வதற்கான அடிப்படை :

அசெனொகொமரால் குறுகிய தெரபியுடிக் அளவும் ஐ.என் ஆர்க்கு சம்மந்தம் இல்லை. அசெனொகொமரால் அளவை இரத்தத்தில் பார்த்தால் நோயாளியை அவர்களுக்கு மூளையில் ஏற்படும் இரத்த கசிவை தவிர்க்கலாம்.

ஆய்வின் நோக்கம் :

நோயாளியின் இரத்தத்தில் உள்ள அசெனொகொமரால் அளவை அறிந்து கொள்வதால் நோயாளிக்கு சரியான அளவு மருந்து கொடுத்து மூளையில் ஏற்பட போகும் இரத்த கசிவை தவிர்க்கலாம்.

ஆய்வில் பங்கு பெறும் நபர்களின் எண்ணிக்கை : 60 பேர்

ஆய்வு மேற்கொள்ளும் இடம் :

கார்டியோ தொராசிக் சர்ஜரி மற்றும் வாஜ்குலார் அறுவை சிகிச்சை

ஆய்வின் பலன்கள் :

நோயாளியின் இரத்தத்தில் உள்ள அசெனொகொமரால் அளவை அறிந்து கொள்வதால் நோயாளிக்கு சரியான அளவு மருந்து கொடுத்து மூளையில் ஏற்பட போகும் இரத்த கசிவை தடுப்பது.

ஆய்வினால் ஏற்படும் அசௌகரியங்கள் மற்றும் பக்க விளைவுகள் : இல்லை

இந்த ஆய்வில் கிடைக்கும் தகவல்கள் ஐந்து வருடங்கள் பாதுகாக்கப்படும். இவை வேறு எந்த ஆய்விற்கும் பயன்படுத்தப்படமாட்டாது. எந்த நிலையிலும் உங்களைப் பற்றிய தகவல்கள் யாருக்கும் தெரிவிக்கப்படமாட்டாது. அவை இரகசியமாக வைக்கப்படும்.

இந்த ஆய்வில் பங்கேற்க ஒப்புக்கொள்ளுவதால் எந்த விதமான பலனும் உங்களுக்குக் கிடையாது. எந்த நேரத்தில் வேண்டுமானாலும் இந்த ஆய்விலிருந்து விலகிக்கொள்ளும் உரிமை உங்களுக்கு உண்டு. ஆய்விலிருந்து விலகிக்கொள்வதால் உங்களுக்கு அளிக்கப்படும் சிகிச்சையில் எந்த வித மாற்றமும் இருக்காது.

இந்த ஆராய்ச்சிக்காக உங்களிடம் சில கேள்விகள் கேட்கப்படும் சில இரத்த மாதிரிகள் எடுக்கப்படும். (இரண்டு முறை 4 ml இரத்தம் எடுக்கப்படும்).

மேலும் இந்த ஆய்வில் பங்கு கொள்வது உங்கள் சொந்த விருப்பம். இதில் எந்த விதக் கட்டாயமும் இல்லை. நீங்கள் விருப்பப்பட்டால், இந்த ஆய்வின் முடிவுகள் உங்களுக்கு தெரியப்படுத்தப்படும்.

ஆய்வாளரின் கையொப்பம் :

தேதி :

ஆய்வுக்குட்படுபவரின் ஒப்புதல் :

நான் இந்த ஆராய்ச்சியின் நோக்கம் மற்றும் அதன் பயன்பாட்டினைப் பற்றி தெளிவாகவும், விளக்கமாகவும் தெரியப்படுத்தப்பட்டுள்ளேன். இந்த ஆராய்ச்சியில் பங்கு கொள்ளவும், இந்த ஆராய்ச்சியின் மரத்துவ ரீதியான குறிப்புகளை வரும் காலத்திலும் உபயோகப்படுத்திக் கொள்ளவும் முழு மனதுடன் சம்மதிக்கிறேன்.

ஆய்வுக்குட்படுபவரின் பெயர், முகவரி :

கையொப்பம் :

தேதி :

ஆய்வாளரின் தொலைபேசி எண் :9566611668

மனித நெறிமுறைக் குழு அலுவலகத்தின் தொலைபேசி எண் : 0422 2570170 EXTN : 5818

MEDICATION HISTORY REVIEW FORM

OP Number :	**Date :**
Patient Name:	**Ward/Dept:**
Age :	**Sex :** M / F
Height (cm) :	**Weight (kg):**

SOCIAL HISTORY

Occupation : _____

Marital Status : _____

Family History : _____

Social Habits		
Diet	☐ Veg	☐ Non -Veg
Coffee/Tea	☐ Yes	☐ No
Smoking	☐ Yes	☐ No
Tobacco	☐ Yes	☐ No
Alcohol	☐ Yes	☐ No

FOR PATIENTS ON ACENOCOUMAROL

HISTORY	YES	NO
1)No of months or years after surgery		
2)No of months or years on acenocoumarol		
3) Any history of bleeding? (ADR)		
4)History of bleeding tendencies or blood disorder		

IMMUNIZATION HISTORY (If any)**:**_____

ALLERGIES :(If any) _____

PAST MEDICAL HISTORY : _____

PAST MEDICATION HISTORY : _____

_____

_____

COMPLIANCE **:** ☐ Yes ☐ No

PREVIOUS LAB DATA (If any**):**_____

OVER THE COUNTER MEDICATIONS (If any**):**_____

_____

PRESENT LAB DATA **:** _____

_____

_____

DIAGNOSIS **:**

_____

TREATMENT

S.No	Drugs	Dose/Dosage	Directions	Indication

Data collected by

Name :

Sign :